CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986 & 22-072

MEDICAL REVIEW(S)

Division of Drug Oncology Products

Acting Deputy Director/Medical Team Leader's Summary Review

NDAs:	21986, 22072
Sponsor:	Bristol Myers Squibb
Drug Product:	Dasatinib
Projected Action Date:	June 28, 2006

Summary

On December 28, 2005, Bristol Myers Squibb submitted this New Drug Application (NDA) for dasatinib, an oral multi-tyrosine kinase inhibitor and a new molecular entity, for:

1) Treatment of adults with chronic, accelerated (AP), or blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib,

2) Philadelphia chromosome-positive (Ph^+) acute lymphoblastic leukemia (ALL) and lymphoid blast (LB) chronic myeloid leukemia with resistance or intolerance to prior therapy.

The NDA efficacy database for CML and Ph^+ALL is comprised of 4 single arm studies in all disease phases and one randomized study in patients with chronic phase (CP) CML. The safety database is comprised of additional studies in healthy volunteers and solid tumors.

During the application review, a few issues were identified and these issues were discussed at an Oncology Drugs Advisory Committee (ODAC) meeting held on June 2, 2006.

The key issues for consideration were:

1) whether a lower starting dose should be evaluated to reduce the toxicity
2) whether sufficient data (magnitude/duration) have been provided to recommend dasatinib for the imatinib resistant population
3) whether sufficient data (magnitude/duration) have been provided to recommend dasatinib for the imatinib intolerant population

ODAC met and voted overwhelmingly to approve the discussed the application. Please see the medical officers' (MO) review for a summary of the discussion and voting.

Application

Chemistry, Manufacturing and Control

Dasatinib is a white to off-white powder and has a melting point of 280°–286° C. SPRYCEL tablets are white to off-white, biconvex, film-coated tablets containing dasatinib and are available in 20 mg, 50 mg, and 70 mg strengths. The tablets are insoluble in water and contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

All inspections have been completed and are acceptable.

For further details, please see Dr. Timmer's Chemistry, Manufacturing, and Control review of this NDA. The reviewer did not identify any required phase 4 commitments.

Pharmacology/Toxicology

Dasatinib is a multi-tyrosine kinase inhibitor, which at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ.

The sponsor conducted acute toxicology, repeat dose toxicology, and safety pharmacology studies. Acute and repeat dose toxicology studies in rats and monkeys revealed gastrointestinal (GI) effects such as (red/liquid feces, hemorrhage, and edema), lymphocytic/ hematopoietic system (lymphoid depletion; bone marrow depletion (rats)), thrombocytopenia (rats), liver (increased AST and ALT (monkeys)); hypertrophy and increased triglycerides (rats), kidneys (tubular dilatation) and additional findings observed only in rats: tubular epithelial vacuolation, increased urinary volume, increased urinary RBC and WBC. In addition, studies in rats revealed cardiotoxicity such as ventricular necrosis, valvular/ventricular/atrial hemorrhage, and cardiac hypertrophy. Increased systolic and diastolic blood pressure recordings were observed in monkeys. Reproductive organ toxicities were observed in rats only (male reproductive system: hemorrhage in epididymis, hemorrhage, and multinucleated cells in testes). Safety pharmacology testing in hERG and rabbit Purkinje fiber assays suggested that dasatinib has the potential to cause QT prolongation. However, QT prolongation was not observed in the EKG evaluations in the toxicology studies conducted in monkeys.

Dasatinib was clastogenic to Chinese Hamster Ovary cells, in the absence or presence of S9 metabolic activation. However, Dasatinib was not mutagenic in the bacterial reverse mutation assays (Ames Test) and did not cause

chromosomal damage in the rat bone marrow micronucleus test, under the conditions of the study. No genetic toxicology studies were conducted with unique human metabolites.

Dasatinib was teratogenic at sub-therapeutic concentrations in rats and rabbits. Embryo-fetal effects, i.e. lethality (rats) and/or abnormalities (rats and rabbits), were manifest at doses that did not cause maternal toxicities and sub-therapeutic exposures. These effects involved: embryo-lethality, increased resorption and decreased mean litter size, and ossification problems.

The proposed labeling includes information in the Warnings section regarding Pregnancy category D (nonclinical teratogenicity findings) and potential impact on male fertility.

For further details, please see Dr. Saber-Mahloogi's Pharmacology and Toxicology review of this NDA. The reviewer did not identify any required phase 4 commitments.

Clinical Pharmacology

Absorption, Distribution, Metabolism, and Excretion
Approximately 0.5 to 6 hours following ingestion, maximal plasma concentrations are achieved. Dasatinib displays dose proportionality (AUC and linear elimination) over range of 15 mg to 240 mg. Ingestion of a high fat meal only slightly increased the mean AUC in healthy subjects administered a single dose of dasatinib at 100mg. The volume of distribution is approximately 2500 L, suggesting that dasatinib is widely distributed. Dasatinib is metabolized primarily by CYP3A4 and is a time-dependent inhibitor; however flavin-containing monooxygenase 3 and uridine diphosphate-glucuronosyl-transferease (UGT) enzymes are also involved. Elimination is primary through the GI tract.

No clinical renal or hepatic impairment studies have been conducted. Analyses of pharmacokinetic demographic data did not reveal any effects of age or gender on dasatinib. No data exists on dasatinib in pediatric patients.

Based on the fact that the major metabolism pathway is CYP3A4, dasatinib plasma levels are expected to increase in the presence of a CYP3A4 inhibitor and decrease in the presence of a CYP3A4 inducer.

Based on the nonclinical data suggesting that dasatinib has pH dependent solubility, studies were performed in healthy volunteers administered either antacids or anti-histamine 2 (H_2) blockers. In both studies, dasatinib C_{max} and AUC were decreased following administration. Co-administration of dasatinib with a CYP3A4 substrate resulted in an increase in mean AUC and C_{max} by 37% and 20% respectively.

The proposed labeling includes information in the Precautions section regarding co-administration of dasatinib with CYP3A4 inducers and inhibitors and in the Drug-Drug Interactions section on co-administration of dasatinib with CYP3A4 inducers, inhibitors, antacids, and H_2 blockers/proton pump inhibitors.

The review team has identified the following required phase 4 commitments:
1. BMS should complete and submit a hepatic impairment study with dasatinib.

2. BMS should submit the ongoing ketoconazole drug-drug interaction study.

Clinical

Please see Drs. Brave, Goodman, and Kaminskas' medical officers' review for background information on CML and treatment options.

This application contains a phase 1 study, 4 international, multicenter, open-label, single arm phase studies in CP CML, accelerated phase (AP) CML, myeloid blast (MB) CML, lymphoid blast (LB) CML, and Ph^+ALL which are ongoing at this time. Data from these single arm trials have approximately 6 months of follow-up. When complete these studies will have 24 months of follow-up. In addition, one ongoing, open-label, randomized trial comparing imatinib at 400 mg twice daily (BID) with dasatinib 70 mg BID for the treatment of patients with CML who have disease that is resistant to imatinib at total doses of 400mg to 600 mg daily. Efficacy endpoints for regulatory consideration differed by disease: primary efficacy endpoint in CP CML is major cytogenetic response (MCyR = complete cytogenetic response CCyR [0% Ph^+ cells] + partial cytogenetic response (PCyR) [1-35% Ph^+ cells) at 12 weeks. The primary efficacy endpoint for regulatory consideration in Advanced Phases is major hematologic response (MaHR= [complete hematologic response (CHR) or no evidence of leukemia (NEL]). Other response categories include minor hematologic response (MiHR) and overall hematologic response (OHR).

Demographic and Disease Characteristics of Enrolled Patients
The demographics of patients enrolled in the studies were somewhat typical of CML and Ph^+ALL. However, only 10% of the patients enrolled were non-Caucasian. All patients had extensive prior treatment, including imatinib (100%), chemotherapy (60%), interferon (75%), hydroxyurea and/or anagrelide (82%), and bone marrow transplant (17%). The table below illustrates the disease and treatment characteristics of the enrolled populations.

Table 1: Disease Characteristics for Enrolled Patients

	Chronic Phase N=186	Accelerated Phase N=107	Myeloid Blast N= 74	Lymphoid Blast N=42	Ph+ ALL N=36
Median time from initial CML					

diagnosis (months)	64	91	49	28	20
Prior Therapy other than Imatinib					
Prior bone marrow transplant (%)	9	18	12	33	42
Prior chemotherapy (%)	43	67	66	79	92
Prior Interferon (%)	70	75	55	48	8
Prior hydroxyurea or anagrelide (%)	86	96	88	79	14
Length of Imatinib Therapy (%)					
< 1 year	20	8	15	48	44
1-3 years	26	24	38	29	53
> 3 years	54	68	47	24	3
Highest Imatinib Dose (%)					
>600 mg	52	59	49	52	47
400-600 mg	48	41	51	45	53
<400 mg	0	0	0	2	0
Best Hematologic Response to Imatinib (%)					
Complete	86	83	84	67	75
No Evidence of Leukemia (NEL)	0	6	5	7	0
No Response	10	9	7	16	8
Unable to Determine	4	2	4	10	17
Best Cytogenetic Response to Imatinib (%)					
Complete	17	10	32	33	42
Partial	16	22	14	10	8
Other	66	65	53	57	50
Reason for Discontinuation of Imatinib	68	93	92	88	94
Resistance	32	7	8	12	6
Intolerance					

Reviewer's Table

Dose

The sponsor conducted a dose-finding study and chose 70 mg BID as the recommended phase 2 dose; however, the study failed to determine the maximally tolerated dose (MTD) and evidence of efficacy was observed at lower dose regimens as shown in the table below. Responses were observed with total doses as low as 30 mg/day in patients with CP CML. Responses were observed with 50 mg BID in patients with all other diseases. These results suggest that patients may achieve response with lower doses than the recommended phase 2 dose.

Table 2: MCyR Responses by Total Daily Dose from Phase 1 study for patients with CP CML

Total Daily Dose*	No. responses/ No. treated	% with Responses
15 mg	0/3	0%
30 mg	1/3	33%
50 mg	1/6	17%
70 - 75 mg	3/10	30%
100 - 105 mg	6/6	100%
140 mg	6/9	67%
180 mg	1/3	33%

* Includes once daily (QD) and BID dosing
Reviewer's Table

Table 3: MaHR Responses by Total Daily Dose from Phase 1 study for patients with all phases of CML except CP CML and Ph^+ALL

Total Daily Dose	No. responses/ No. treated	% with Responses
35 mg BID	0/1	0%
50 mg BID	3/8	38%
70 mg BID	5/17	29%
90 mg BID	2/11	18%
120 mg BID	1/7	14%

Reviewer's Table

Efficacy

The table below shows the efficacy results by disease category from all phase 2 studies. The bolded results are those used for a regulatory decision.

Table 4: Summary of Cytogenetic and Hematologic Responses – Percentages of Subjects with Responses – All Treated Subjects in the Single-Arm Phase 2 Studies

	CA180013 Chronic (N = 186)	CA180005 Accelerated (N = 107)	CA180006 Myeloid Blast (N = 74)	CA180015 Lymphoid Blast (N = 42)	CA180015 Ph^+ ALL (N = 36)
Hematologic Response Rate (%)					
OHR (95% CI)	NA	80 (72 - 87)	53 (41 - 64)	36 (22 - 52)	47 (30 - 65)
MaHR (95% CI)	NA	**59 (49 - 68)**	**32 (22 - 44)**	**31 (18 - 47)**	**42 (26 - 59)**
CHR (95% CI)	90 (85-94)	33 (24-42)	24 (15-36)	26 (3-17)	31 (16-48)
NEL (95% CI)	NA	26 (18-36)	8 (3-17)	5 (0.6-16)	11 (3.1-26)
MiHR (95% CI)	NA	21 (14 - 31)	20 (12 - 31)	5 (0.6 - 16)	6 (0.7 -19)
Cytogenetic Response Rate (%)					
MCyR (95% CI)	**45 (37 -52)**	31 (22-41)	30 (20 - 42)	50 (34 - 66)	58 (41 - 75)
CCyR (95% CI)	33	21	27	43	58

Reviewer's Table

The table below illustrates available information regarding the median duration of response by disease category. Although the median duration of response cannot be estimated for enrolled patients with CP CML, AP CML, and MB CML, approximately 100% of the responders in these disease categories remain in response at 6 months.

Duration of Response

The table below illustrates the median duration of response data. No patient had treatment for greater than 1 year. Thus the

Table 5: Median Duration of Response

	Chronic Phase	Accelerated Phase	Myeloid Blast	Lymphoid Blast	Ph + ALL
Median duration of response in months, (95% CI)	Not reached*	Not reached*	Not reached*	3.7 (2.8 – not reached)	4.8 (2.9- not reached)

* Approximately 100% of responders are in response at 6 months.

Reviewer's Table

The sponsor enrolled 2 categories of patients in these studies: those considered resistant to imatinib and those considered intolerant to imatinib. Imatinib resistance was defined as:
1) progression of CP-CML on imatinib ≥ 400 mg/day, or
2) progression of AP-CML on imatinib ≥ 600 mg/day, or
3) MBP- or LBP-CML after at least 4 weeks of treatment with imatinib ≥ 600 mg/day.

Imatinib intolerance was defined as:
1) imatinib-related toxicity that led to imatinib discontinuation, or
2) ability to tolerate imatinib at only ≤ 400 mg/day.

For more detailed information on the definitions of resistant and intolerant please see the Medical Officer's review.

The table below illustrates the response rates for the imatinib-resistant and imatinib-intolerant populations. The number of intolerant patients enrolled per study except for the CP CML studies was less than 10%. The numbers of imatinib intolerant subjects were small in the other studies and appear insufficient to draw valid conclusions.

Table 6: Summary of MCyR and MaHR Responses in Imatinib-Intolerant and Imatinib-Resistant Subjects in All Studies

Disease phase	Intolerant N = 94		Resistant N = 457	
	MCyR	MaHR	MCyR	MaHR
Chronic	49/67 (73%)		62/181 (34%)	
Accelerated		7/12 (58%)		62/106 (58%)
Myeloid Blast		1/7 (14%)		30/90 (33%)
Lymphoid Blast		2/6 (33%)		14/41 (34%)
Ph+ ALL		2/2 (100%)		14/39 (36%)

Reviewer's Table

Safety/Dose Regimen Issues
As illustrated in the table below, dose modifications were observed in all populations studied with dose reductions occurring in 11-50% of patients and dose interruption in 57-82% of patients. Dose adjustments were more common in patients with earlier stage disease, largely due to dose modifications for hematologic toxicity. Dasatinib was discontinued due to adverse events in 4-6% of patients with CP CML and AP CML, and in 13-15% of patients with MB CML, LB CML and Ph + ALL.

Table 7: Dose Adjustments Based on 70 mg BID Dosing

Disease Phase	Dose Reduction	Dose Interruption
CP	50%	82%
AP	45%	73%
MB	35%	74%
LB	11%	57%
Ph+ALL	30%	68%

Reviewer's Table

Overall Safety Assessment

In the original submission contained 489 patients with all stages of CML and Ph + ALL in the safety population (214 patients with CP CML, 110 with AP, 84 patients with MB CML and 81 patients with LB CML or Ph + ALL). All these patients received a starting dose of dasatinib of 70 mg BID. Most patients (57%) had 3-6 months of exposure to dasatinib, while only 32% were treated for less than 3 months. The rest (11%) were treated for more than 6 months.

The most common adverse events included gastrointestinal events (diarrhea (47%), nausea (31%), abdominal pain (25%), and vomiting (22%)) and constitutional events (pyrexia (39%), headache (38%), fatigue (34%), asthenia (22%) and anorexia (15%)). Fluid retention events such as peripheral edema (26%) and pleural effusion (17%) were also very common. Overall, edema of any type occurred in 40% of all patients and bleeding events of any type in 34%. The majority of bleeding events were grade 2 or less.

The most common grade 3/4 adverse events were hematologic abnormalities (neutropenia and thrombocytopenia). Incidences of grade 3 or 4 severity occurred in approximately 45-80% of patients, and grade 3 or 4 anemia in 18-66%. These abnormalities were least common in CP CML and of similar incidence in all other stages of disease.

Other common grade 3/4 events included neutropenic fever (10%), bleeding events (10%), pyrexia (7%), dyspnea (6%), pleural effusion (5%), and diarrhea (5%).

Although grade 3-4 bleeding was seen in 10% or less of enrolled patients, fatal bleeding events occurred. Other significant adverse events included CNS hemorrhages occurring in 6 patients, 5 of which were fatal. All but one event occurred in patients with advanced disease.

Cardiac failure occurred in 4% of patients; most of these patients had cardiac risk factors such as hypertension. QTc prolongation reported either as an adverse

event or on central laboratory reading (> 500 msec) was reported in 2-3% of patients. The average increase in QTcF from baseline was 3-6 milliseconds.

No new safety issues were identified in the Safety Update.

The Medical Officer Review team recommends information in the Precautions section of the labeling for myelosuppression, bleeding related events, fluid retention, and QT prolongation.

For further details, please see the Medical Officers' review of this NDA.

Division of Scientific Investigations

The Division of Scientific Investigations (DSI) audited 4 sites (2 US and 2 non-US). Data from all but one site were deemed reliable. Data from the remaining site was deemed acceptable. The number of patients audited at that site and discovered to have problems is small and unlikely to influence the outcome if removed from the analyses. Thus, the application is approvable based on the DSI investigation.

For additional details, please see the Division of Scientific Investigations report: Preliminary Evaluation of Clinical Inspections, Pending Receipt of all EIRs.

Division of Drug Medication Errors and Technical Support (DMETS) and Division of Drug Marketing, Advertising, and Communications (DDMAC)

Both divisions reviewed the proposed trade name SPRYCEL. The DDMAC review did not recommend approval of the name because the Division stated the

The DMETS review stated the Division had no objections to the use of the name and did not think there would be sound-alike or look-alike confusion. DMETS had additional recommendations for labeling that were sent to the company.

The review staff carefully considered

Therefore, the team recommends that the company be permitted to use SPRYCEL as its trademark name.

<u>Ongoing Studies</u>

The single arm studies submitted had treatment durations of 6 months or less. Due to the short duration of these studies, the sponsor will need to provide additional follow-up data from these studies at completion. These requests will be part of the phase 4 commitment.

Discussion

Several issues are germane to this application. The sponsor's results from the 4 multicenter, single arm, phase 2 studies suggest that dasatinib is efficacious for

1) Treatment of adults with chronic, accelerated, or blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib,

2) Philadelphia chromosome-positive (Ph^+) acute lymphoblastic leukemia (ALL) and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy.

The question arises as to the type of approval (regular or accelerated) this application can receive. For CP, AP, BP CML the Agency has accepted response rates (MCyR and MaHR) with limited duration for accelerated approval. For acute leukemia, the Agency has accepted complete response rate of limited duration for full approval. Due to the distinctions in approvals types, this application may receive, the application was split into two based on indication: one for CML and the other for Ph^+ALL.

The Sponsor's recommended dasatinib starting dose for patients with all phases of CML and with Ph+ ALL is 70 mg BID. Many patients receiving 70 mg BID required dose interruptions and reductions due to toxicity. Responses were also seen at lower doses in a limited number of patients in the phase 1 study. Currently, not enough data exists to recommend a starting dose other than 70 mg BID. The sponsor should perform additional dose regimen studies to provide more information on the safety and efficacy of dasatinib at a lower dose (e.g. 50 mg BID).

Conclusions and Recommendations

The dasatinib application (21986) should receive Subpart H approval for the indication for the treatment of all phases of CML. The dasatinib application (22072) should receive regular approval for the indication for the treatment of Ph^+ALL.

Due to the accelerated approval, the sponsor will be required to submit the data from the ongoing phase 2 studies in order to convert to regular approval.

Other phase 4 commitments that will be requested from the sponsor include:

1) Submission of a hepatic impairment study
2) Submission of an ongoing ketaconazole drug-drug interaction study
3) Submission of data from an ongoing study of dose and regimen where the study will evaluate MCyR rates for 50 mg BID, 100 mg once daily, 70 mg BID, and 140 mg once daily regimens.

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/s/

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CLINICAL REVIEW

Application Type	21-986
Submission Number	SN-000
Submission Code	
Letter Date	December 28, 2005
Stamp Date	
PDUFA Goal Date	June 28, 2006
Reviewers' Names	Michael Brave, M.D., Vicki Goodman, M.D. and Edvardas Kaminskas, M.D.
Review Completion Date	June 22, 2006
Established Name	Dasatinib (BMS-354825)
Proposed Trade Name	Sprycel™
Therapeutic Class	Antineoplastic
Applicant	Bristol-Myers Squibb
Priority Designation	P
Formulation	Tablets
Dosing Regimen	Oral
Indication	Chronic Myelogenous Leukemia resistant to or intolerant of imatinib mesylate
Intended Population	Adults

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LIST OF ABBREVIATIONS

AA	accelerated approval
AP CML	accelerated phase CML
CP CML	chronic phase CML
MB CML	myeloid blast phase CML
LB CML	lymphoid blast CML
MaHR	major hematologic response
OS	overall survival

Other abbreviations are shown in Sponsor's List of Abbreviations on pp. 9-10.

13 LIST OF ABBREVIATIONS

Term	Definition
ALL	acute lymphoblastic leukemia
AE(s)	adverse events(s)
ANC	absolute neutrophil count
BID	twice daily
BMS	Bristol-Myers Squibb
CCyR	complete cytogenetic response
CHR	complete hematologic response
CK	creatine kinase (creatine phosphokinase)
CK-MB	subtype (isoenzyme) of CK from heart muscle
CML	chronic myeloid leukemia
CRF	case report form
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	The Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MCyR	major cytogenetic response
MTD	maximum tolerated dose
NCI	National Cancer Institute
NEL	no evidence of leukemia
OHR	overall hematological response
PCR	polymerase chain reaction
PCyR	partial cytogenetic response
Ph	Philadelphia
Ph+ ALL	Philadelphia chromosome positive acute lymphoblastic leukemia
PK	Pharmacokinetics
Q-RT-PCR	quantitative-real-time polymerase chain reaction
QD	once daily
QT	the interval between the beginning of the Q-wave and the end of the T-wave on an electrocardiogram
QT_c	corrected Q to T wave interval on electrocardiogram
RTC	return to chronic phase
SAE	serious adverse event
SRC	a protein tyrosine kinase
WBC	white blood cell
WOCBP	women of childbearing potential

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Accelerated approval should be granted for dasatinib for use in the treatment of adults with chronic phase (CP), accelerated phase (AP), or myeloid or lymphoid blast (MB or LB) phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate.

Regular approval should be granted for dasatinib for use in the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL) with resistance or intolerance to prior therapy.

Patients with CML or Ph^+ ALL that is resistant to imatinib or who can not tolerate imatinib have limited therapeutic options, and no drugs are currently approved for these indications. The clinical data presented in the NDA provides substantial evidence of effectiveness of dasatinib in the form of hematologic and cytogenetic responses which appear to be durable and to decrease the risk of disease progression. Final characterization of this durability in CML patients will require a longer follow-up period; these results may permit regular approval. The safety profile of dasatinib is acceptable, given the seriousness of these disease entities.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The sponsor should provide periodic safety reporting and continue post-marketing surveillance activities.

1.2.2 Required Phase 4 Commitments

- Completion of ongoing, single-arm Phase 2 studies in patients with CP CML (CA180013), AP CML (CA180005), and MB CML (CA180006) who are resistant to or intolerant of imatinib mesylate, and in patients with LB CML (CA180015) who are resistant to or are intolerant of prior therapy.
- Submission of the ongoing study of ketoconazole on dasatinib PK.
- Submission of ongoing study of dasatinib PK in hepatic impairment.

1.2.3 Other Phase 4 Requests

- Completion of ongoing, single-arm Phase 2 studies in patients with Ph^+ ALL (CA180015) who are resistant to or are intolerant of prior therapy.

- Completion of the four-arm study (CA180034) examining optimal dose and schedule (100 mg QD vs. 140 mg QD vs. 50 mg BID vs. 70 mg BID) in CP CML.
- An *in vivo* study of dasatinib as inhibitor of P-gp.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Dasatinib is an orally administered inhibitor of several tyrosine kinases including BCR-ABL, the molecular hallmark of CML. Dasatinib was evaluated for the treatment of adults with all phases of CML and Ph^+ ALL. Patients had to be resistant to or intolerant of prior therapy including imatinib.

Safety and efficacy data were generated by one Phase 1 dose escalation study and from five multicenter Phase 2 studies which enrolled a total of 1,104 patients. These include 551 patients with efficacy data, including all patients treated in the Phase 1 dose escalation study, and 489 patients who are included in the safety database. All patients in the Phase 2 studies were treated with dasatinib starting dose of 70 mg BID.

Interim results are presented in this submission on patients with a minimum 6 months of follow-up after the start of dasatinib therapy. Median durations of treatment were 5.6 months, 5.5 months, 3.5 months, 2.8 months, and 3.2 months in patients with CP CML, AP CML, MB CML, LB CML, and Ph^+ ALL, respectively.

Median ages of patients in the CP CML, AP CML and MB CML studies were 55 to 59 years (range 21-86). The median age of patients in the LB CML/Ph^+ ALL study was 47 with an age (range 15-85). Male to female ratios were about 1:1 in all populations except in Ph^+ ALL, where it was 1.8:1. About 90% of the patients were Caucasian, and about 10% were Black or Asian. CP CML patients tended to have better performance statuses than patients with advanced stages of CML and Ph^+ ALL.

Most patients had relatively long disease histories. Median times since the initial diagnosis were 64, 91, and 49 months in CP CML, AP CML, and MB CML patients, respectively, and 28 and 20 months in LB CML and Ph^+ ALL patients, respectively.

The patient population studied had extensive prior treatment, including with imatinib (100%), chemotherapy (60%), interferon (75%), hydroxyurea and/or anagrelide (82%), and bone marrow transplantation (17%). Imatinib had been discontinued because of resistance in 76% of patients and because of intolerance in 24%. Approximately half to 90% of patients, depending on the disease under study, had received prior imatinib for at least one year, and between 24% and 68% had received at least 3 years. The maximum imatinib dose had been 400 – 600 mg per day in about one-half of patients and > 600 mg per day in the other half.

1.3.2 Efficacy

Evidence of dasatinib efficacy is based on the results of 4 single-arm Phase 2 studies, one two-arm, randomized Phase 2 study, and one Phase 1 dose escalation study. The primary efficacy endpoint in CP CML studies was major cytogenetic response (MCyR), defined as elimination or substantial diminution (by at least 65%) of Ph^+ hematopoietic cells. Co-primary endpoints in AP CML, MB CML, and LB CML/Ph^+ ALL studies were hematologic responses. Major hematologic response (MaHR) was defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL), and overall hematologic response (OHR) was defined as a major (MaHR) or minor (MiHR) hematologic response.

Primary efficacy endpoints:

- CP CML
  - In Study CA180013, 84 (45%) of 186 patients achieved a MCyR.
  - In Study CA180017, 10 (45%) of 22 patients treated with dasatinib achieved a MCyR, compared to 3 (21%) of 14 patients treated with imatinib 400 mg BID.
- AP CML (Study CA 1800005)
  - Sixty three (59%) of 107 patients achieved a MaHR.
  - Eighty six (80%) patients achieved an OHR.
- MB CML (Study CA 1800006)
  - Twenty four (32%) of 74 patients achieved a MaHR.
  - Thirty nine (53%) achieved an OHR.
- LB CML (Study Ca180015)
  - Thirteen (31%) of 42 patients achieved a MaHR.
  - Fifteen (36%) achieved an OHR.
- Ph^+ ALL (Study CA180015)
  - Fifteen (42%) of 36 patients achieved a MaHR.
  - Seventeen (47%) achieved an OHR.

Secondary efficacy endpoints:

- CP CML
  - CHR rate was 90%.
  - Median time to CHR was 15 days, and 99% of patients remain in response (the longest duration is 7.6+ months).
  - Median time to MCyR was 85 days, and 100% of patients remain in response (the longest duration is 4.6+ months).
- AP CML
  - MCyR rate was 31%.
  - Median time to MaHR was 57 days, and 98% of patients remain in response (the longest duration is 9.5 months).
- MB CML
  - MCyR rate was 30%.
  - Median time to MaHR was 57 days, and 100% of patients remain in response (the longest duration is 7.8 months).
- LB CML
  - MCyR rate was 50%.

- Median time to MaHR was 33 days.
- Median duration of MaHR was 3.7 months.

- Ph^+ ALL
  - MCyR rate was 58%.
  - Median time to MaHR was 54 days.
  - Median duration of MaHR was 4.8 months.

The efficacy data demonstrate:

- Dasatinib treatment resulted in hematologic and cytogenetic responses in patients with all phases of CML and with Ph^+ ALL who are imatinib-resistant or intolerant of imatinib.
- Most hematologic and cytogenetic responses occurred during the first 3 months of treatment.
- MCyR, MaHR, and OHR were associated with lower probability of disease progression.
- CP CML patients intolerant to imatinib achieved higher hematologic and cytogenetic response rates than those with imatinib-resistance. Numbers of imatinib intolerant DFSpatients in other studies were insufficient to draw reliable conclusions.
- No age- or gender-related response differences were apparent.

Limitations of available efficacy data:

- The four major Phase 2 trials had single-arm designs because it was deemed that no effective control therapy was available.
- The primary endpoints chosen depended upon the disease phase being studied – cytogenetic response in CP CML and hematologic response in advanced-phase CML and in Ph^+ ALL. Because marrow fibrosis and poor marrow reserves can impede cytogenetic analysis, cytogenetic response was a secondary efficacy endpoint in studies of advanced phase disease.
- The efficacy conclusions are based on interim data of ongoing studies. The response rates were calculated, but the median duration of these responses had not been reached in 3 of the 5 patient populations studied.
- The dose determination study did not define a dose-response relationship. The optimal dose with respect to efficacy appears to be 50 - 70 mg BID in all patient populations studied.

Reviewer's efficacy conclusions:

- Dasatinib produced hematologic and cytogenetic responses in all patient populations studied
- Response rates were higher in imatinib-intolerant than in imatinib-resistant CP CML patients.
- At the time of this interim analysis, responses appear relatively durable and associated with lower incidence of disease progression.
- Responses in imatinib resistant or intolerant CP CML, AP CML, and MB/LB CML patients, who have limited treatment options, are reasonably likely to predict clinical benefit and therefore support accelerated approval.
- Responses in Ph^+ ALL patients, who historically have an extremely poor prognosis, constitute clinical benefit and therefore support regular approval.

Role of dasatinib in the existing treatment armamentarium:

- Dasatinib is an effective drug in patients with all phases of CML and with Ph^+ ALL who are resistant to or intolerant of imatinib and who, therefore, have limited treatment options.

1.3.3 Safety

Four hundred and eighty nine patients with all stages of CML and Ph^+ ALL constituted the safety population. These included 214 patients with CP CML, 110 with AP CML, 84 with MB CML and 81 with LB CML or Ph^+ ALL. All these patients received a starting dose of dasatinib of 70 mg BID.

Most patients (57%) had between 3 and 6 months of exposure to dasatinib. Thirty two percent had been treated for less than 3 months and 11% had been treated for more than 6 months.

Dose modifications were common in all populations studied with dose reductions required in 21-50% of patients and dose interruption in 68-82% of patients. Dose modifications were more common in patients with earlier stage disease, largely due to hematologic toxicity. Dasatinib was discontinued due to adverse events (AEs) in 4-6% of patients with CP CML and AP CML, and in 13-15% of patients with MB CML, LB CML and Ph^+ ALL.

The most common AEs included gastrointestinal events such as diarrhea (47%), nausea (31%), abdominal pain (25%), and vomiting (22%) and constitutional events such as pyrexia (39%), headache (38%), fatigue (34%), asthenia (22%) and anorexia (15%). Fluid retention events such as peripheral edema (26%) and pleural effusion (17%) were also common. Overall, edema of any type occurred in 40% of all patients and bleeding events of any type in 34%.

The most common grade 3/4 AEs were hematologic, including neutropenia and thrombocytopenia in approximately 45-80% of patients, and anemia in 18-66%. These events were less common in CP CML patients than in those with advanced-stage CML or Ph^+ ALL. Other common grade 3/4 events included neutropenic fever (10%), bleeding events (10%), pyrexia (7%), dyspnea (6%), pleural effusion (5%), and diarrhea (5%).

Other significant AEs included CNS hemorrhages in 6 patients, 5 of which were fatal. All but one CNS hemorrhage occurred in patients with advanced disease. Cardiac failure occurred in 4% of patients; most of these patients had cardiac risk factors such as hypertension. QTc prolongation reported either as an adverse event or on central laboratory reading (> 500 msec) was reported in 3% of patients. The average increase in QTcF from baseline was 3-6 milliseconds.

1.3.4 Dosing Regimen and Administration

The Sponsor's recommended dasatinib starting dose for patients with all phases of CML and with Ph^+ ALL is 70 mg BID. Responses were also seen at lower doses in a limited number of patients. There are currently not enough data to recommend a starting dose other than 70 mg BID. However, since many patients receiving 70 mg BID required dose interruptions and reductions due to toxicity, the reviewers recommend that the sponsor study the safety and efficacy of dasatinib at a lower dose (e.g. 50 mg BID).

1.3.5 Drug-Drug Interactions

- Dasatinib is metabolized mainly by CYP3A4. Drugs that inhibit CYP3A4 activity decrease the rate of dasatinib metabolism and increase dasatinib plasma concentrations.
- Dasatinib is an inhibitor of CYP3A4 and may decrease the clearance of drugs primarily metabolized by CYP3A4.
- CYP3A4 inducers, such as rifampicin, decrease dasatinib plasma concentrations.
- Dasatinib increases plasma concentrations of CYP3A4 substrates, such as simvastatin.
- Antacids and proton pump inhibitors result in reduced plasma concentrations of dasatinib.

1.3.6 Special Populations

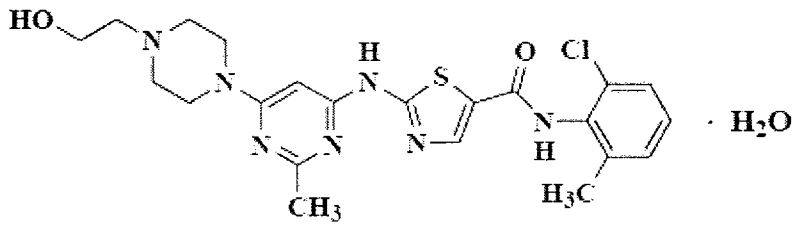
- No age- or gender-related differences in efficacy or safety of dasatinib were apparent.
- No conclusions can be made on any race-related differences in efficacy or safety of dasatinib, because fewer than 10% of patients in clinical studies were non-White.
- Dasatinib has not been studied in pediatric populations.
- Dasatinib has not been studied in patients with hepatic or renal impairment.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The chemical name for dasatinib is *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is $C_{22}H_{26}ClN_7O_2S \cdot H_2O$. The formula weight is 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib drug substance has the chemical structure shown in Figure 1.

Figure 1. Chemical structure of dasatinib



Dasatinib competes with ATP for the ATP-binding site in the kinase domain of selected protein tyrosine kinases (PTKs). It inhibits five PTK families: SRC family (IC_{50} SRC = 0.55 nM, LCK = 1.1- nM, YES = 0.41 nM, FYN = 0.2 nM); BCR-ABL (3 nM); c-KIT (22 nM); EPHA2 (17 nM) and PDGFβ receptor (28 nM).

Compared to imatinib, it is more potent in vitro against BCR-ABL and more cytotoxic against most BCR-ABL dependent leukemic cell lines. This difference may stem from its ability to bind to both active and inactive conformations of c-ABL, whereas imatinib binds only the inactive state.

Imatinib mesylate is currently the only available inhibitor of the BCR-ABL tyrosine kinase. Efficacy is greatest in early CP CML patients, with 95% achieving CHR and 85% MCyR.[1] Imatinib also induces MCyR in 60% of CP-CML patients within 18 months of interferon-α failure.[2] Superior overall survival is difficult to demonstrate because of crossover and high response rates among patients who receive imatinib second-line. In contrast, only 8% and 16% of patients with BP CML achieve these forms of response,[3] and responses are rarely sustained.[4] Preliminary data suggest that imatinib in combination with multiagent cytotoxic chemotherapy is associated with acceptable 30-day mortality.[5]

Imatinib initially received Accelerated Approval for treatment of CML in MBP, AP, and CP after failure of IFN-α on May 10, 2001. This approval was based on hematologic and cytogenetic responses in three nonrandomized, single-arm trials including a total of 1,027 CML patients.[6] Two-year follow-up data from those studies showing high rates of PFS and OS led to the

conversion of imatinib from accelerated to regular approval on December 5, 2003 for the treatment of adults with any-phase CML after failure of IFN-α. Imatinib also received AA for treatment of newly diagnosed CML on December 20, 2002; this indication has not yet been converted to regular approval.[7]

Imatinib is indicated for the treatment of

1. Newly diagnosed adult patients with Ph^+ CP CML.
2. Patients with Ph^+ CML in BP, AP, or in CP after failure of interferon-α.
3. Pediatric patients with Ph+ CP CML whose disease has recurred after stem cell transplant or who are resistant to interferon-α.

2.2 Currently Available Treatment for Indication

No therapy has been approved for the treatment of any phase imatinib-resistant or intolerant CML. Patients with imatinib-resistant CML receive a variety of therapies including experimental therapies.

2.2.1 Chronic Myeloid Leukemia (CML) and Imatinib Resistance

CML is a clonal disease of the hematopoietic stem cell, characterized by a reciprocal chromosomal translocation t(9;22)(q34;q11) which forms the Philadelphia chromosome (Ph^+) and creates a novel fusion gene BCR-ABL. CML is diagnosed in approximately 4,300 patients each year in the United States and accounts for 14% of adult leukemias. The median age at presentation is 45 to 55 years, with a third of patients older than 60 years.

CML has three phases: chronic, accelerated, and blastic. Patients with CML may manifest biphasic or triphasic disease. Chronic phase (CP) CML is characterized by 15% or fewer blasts and promyelocytes in the peripheral blood and bone marrow. Accelerated phase (AP) and blast phase (BP) CML are characterized by 16-30% and >30% blasts in either the peripheral blood or bone marrow, respectively. In addition, patients in the accelerated or blast phase may have extramedullary disease.

Most patients are diagnosed in CP. The clinical onset of CP CML is often insidious as patients are often asymptomatic at the time of diagnosis; whereas patients with AP or BP may present with fatigue, malaise, weight loss or have symptoms related to splenic enlargement. Less frequently patients with advanced disease present with myelosuppression (e.g. infections, thrombosis, or bleeding) or manifestations of leukostasis (e.g., cerebrovascular accidents).

The median survival is 4 to 6 years for all patients with CML, with a range of less than 1 year to more than 10 years. However, once patients develop BP disease, survival is less than 1 year and usually only a few months.

In 2001, the US Food and Drug Administration granted accelerated approval to imatinib mesylate for the treatment of patients with any phase CML after failure of interferon-α. Approval was based on hematologic and cytogenetic responses in three single-arm trials in over 1,000

CML patients. The two-year follow-up data from those studies showing continued high rate of durable responses led to the conversion of imatinib from accelerated to regular approval.

2.2.2 Currently available treatment of imatinib-resistant CML

2.2.2.1 Allogeneic hematopoietic stem cell transplantation

Treatment of CML is usually initiated when the diagnosis is established. The only proven potentially curative treatment of CML is allogeneic hematopoietic stem cell transplantation (HSCT). Approximately 65% of patients who receive a transplant from a matched sibling donor become long-term survivors with no evidence of BCR-ABL by any available test, including RT–PCR. The efficacy of stem-cell transplantation appears to depend in part upon a graft-versus-leukemia effect, as supported by the observation that donor lymphocyte infusions reinduce remission in some patients who relapse to CP-CML post-transplantation.

Allogeneic HSCT is associated with 15% to 30% treatment-related mortality, depending on the donor type (sibling or unrelated), recipient's age, stage of disease, genders of the donor and the recipient (same or different), and time interval from diagnosis to transplantation.[8] Approximately 45 % of CML patients are under the age of 60 years (the upper age limit for transplantation at many centers) at the time of diagnosis. Of them, 30 % have an HLA-matched sibling donor, and approximately 80 % of the remainder have an acceptable unrelated donor. Thus, transplantation is an option for about 40 % of patients with CML.

Preliminary data suggest that nonmyeloablative HSCT using reduced-intensity regimens designed to eliminate malignant cells through a graft-versus-leukemia effect without causing complete aplasia, is effective and better tolerated than myeloablative procedures for CP CML patients with a matched donor.[9]

2.2.2.2 Interferon-α

Interferon-α is an antiproliferative and immunomodulatory protein introduced in the mid-1980s. It is currently approved for Ph^+ CP CML patients who are minimally pretreated (within 1 year of diagnosis).

In randomized phase 3 studies, interferon-α induced a MCyR in 6 to 19% of CP CML patients after a median time of approximately 18 months.[3-6] Ten-year overall survival (OS) from the time of first CCyR is 62 to 82%, and the majority of long-term survivors have no evidence of *bcr/abl* by any available test.[10-17]

A meta analysis of 1554 patients enrolled in 7 randomized trials that began before 1990 concluded that interferon-α prolonged OS of CML patients compared to hydroxyurea ($P = 0.001$) or busulfan ($P = 0.0007$). Five-year OS rates were 57% with interferon-α and 42% with chemotherapy ($P < 00001$).[18]

Subsequent phase 3 studies showed that the addition of cytarabine to interferon-α improves rates of CHR and MCyR. However, results varied as to whether the combination further improved OS.[19,20]

In the Randomized Study of Interferon and STI-571 (IRIS) study, 11 patients who failed first-line therapy with imatinib (6 for disease progression, 4 for intolerance, and 1 for failure to achieve a MCyR at 12 months) crossed over to interferon-α plus cytarabine. Three (27%) of these 11 patients attained CHR and none attained MCyR.[Error! Bookmark not defined.] No data are available regarding the safety or efficacy of interferon-α monotherapy following imatinib failure.

Because of the aggressiveness of advanced-phase CML, interferon is often not feasible in that setting. The largest report was a retrospective review of 100 patients in which 50% attained CHR and 17% attained a MCyR (5% CCyR).[21] There were no data on the characteristics of these patients, so these results must be interpreted with caution. There are no reports on the efficacy of interferon-α in patients with myeloid or lymphoid blast crisis.

2.2.2.3 Imatinib mesylate dose escalation

The imatinib product label recommends starting single-agent therapy at 400 mg daily for adult patients with CP-CML and 600 mg daily for adult patients with AP- or BP CML. Physicians are advised to consider a dose increase to 600 mg in adults with CP CML or to 800 mg (as 400 mg twice daily) in adults with AP- or BP CML in the event of disease progression, failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6-12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

A substantial fraction of patients appear to respond to escalations of imatinib, although these responses are rarely durable, and patients may have significant difficulty tolerating higher doses.[22,23]

Reviewer's Comments: Therapeutic options for patients with imatinib-resistant/refractory CML are limited and suboptimal.

2.3 Availability of Proposed Active Ingredient in the United States

Dasatinib is available under a treatment IND for patients with AP- or BP CML or Ph^+ ALL who are resistant to or intolerant of imatinib mesylate.

2.4 Important Issues With Pharmacologically Related Products

Dasatinib is pharmacologically related to imatinib mesylate (Gleevec®), also an inhibitor of BCR-ABL kinase. Resistance to imatinib develops over time.

2.4.1 Definition of imatinib resistance

Imatinib resistance can be defined operationally as an incomplete hematologic response in patients with CP CML or as a failure to return to chronic phase for patients with CML in AP or BP or Ph^+ ALL.[24]

2.4.2 Incidence of imatinib resistance

Development of imatinib resistance is relatively unusual in early CP CML patients, whereas its estimated 2-year incidence is 10-20% in CP CML post-interferon-α failure, 40-50% in AP CML, and 70-80% in BP CML or Ph^+ ALL. In one study of 141 patients with CP CML responding to imatinib after failure of interferon-α, 11% and 15% developed resistance by 12 and 18 months, respectively. Risk factors for the development of imatinib resistance were the presence of cytogenetic clonal evolution and failure to achieve a MCyR.[25]

2.4.3 Mechanisms of imatinib resistance

BCR-ABL exists in equilibrium between an "open" catalytically active conformation and a "closed" inactive state. Crystallographic studies show that imatinib binds to the ATP-binding site of c-ABL only when the catalytic domain of the kinase is closed and stabilizes the protein in its inactive conformation.[26]

The majority of CML patients with imatinib resistance have secondary *bcr-abl* mutations. These cause imatinib resistance by either impairing the ability of the kinase to adopt the closed conformation to which imatinib binds or by directly interfering with drug binding.

Secondary *bcr-abl* mutations conferring imatinib resistance tend to cluster in four regions.[27-33]

1. The P-loop is a conserved, flexible, glycine-rich structure that serves as a binding site for nucleotide-phosphate groups of ATP. P-loop mutations include Y253F, G250E, E255K and Q252H, and cause resistance by shifting the equilibrium of the ABL kinase towards the active state. P-loop mutations are common and associated with a poor prognosis.

2. The T315 proximal region contains non-conserved residues that directly bind imatinib without significantly affecting the binding of ATP. Mutations in this region include T315I and F317L.
3. The catalytic domain involves residues 351-359. Mutations in this region include M351T, E355G and F359V.
4. The A-loop connects the N- and C-terminal lobes of the kinase domain. A-loop mutations such as H396R, V379I, and L378M prevent the kinase from achieving the conformation required to bind imatinib.

Imatinib resistance is occasionally caused by BCR-ABL protein overexpression due to *bcr-abl* gene amplification, recognized by interphase fluorescence in situ hybridization using *bcr* and *abl* probes. Unlike patients with *bcr-abl* mutations, who may be completely imatinib resistant, those

with BCR-ABL overexpression due to gene amplification often respond to increased doses of imatinib.[34] Finally, imatinib resistance caused by P-glycoprotein overexpression[35] or α_1-acid glycoprotein effects[36] is thought to be rare.

2.5 Presubmission Regulatory Activity

Mar. 11, 2003 The Applicant submitted an initial Investigational New Drug application for dasatinib.

April 2, 2003 The FDA notified the Applicant that it was reasonably safe to initiate clinical studies as outlined in the Investigational New Drug application for dasatinib.

Dec. 15, 2004 An End-of-Phase 1 meeting was held at which BMS advised DDOP of their intent to submit at the end of 2005 an NDA for accelerated approval (AA) of single-agent dasatinib as therapy for imatinib-resistant CML and Ph^+ AML, based on 6 clinical pharmacology studies and 5 clinical phase 2 studies.

DDOP advised the sponsor that in order to receive AA:

- They must show an improvement in efficacy and/or toxicity over available therapy (i.e. interferon-α) in this setting. Compelling results from a single-arm trial could serve this purpose.
- CHR and MCyR could be adequate primary endpoints, depending on the magnitude of the benefit. The sponsor claimed that assessing these endpoints beyond 3 months in a randomized trial would be difficult because of crossover.
- Definitions of imatinib-resistance and intolerance should be prespecified and patients clearly identified as belonging to one of these groups.
- A first-line treatment trial of dasatinib versus imatinib with a minimum follow-up of 24 months should be planned to demonstrate clinical benefit in chronic-phase CML.

DDOP and the sponsor agreed on the ECG monitoring and dose modification plan, and on deferral of pediatric studies.

The Clinical Pharmacology Review Team had additional recommendations regarding studies of active dasatinib metabolites and the effects of CYP3A4 induction, P-gp inhibition, and hepatic impairment.

DDOP referred the sponsor to regulations and guidances in the areas of:

- Timing of pediatric studies
- Special protocol assessment
- Submission of trial information to NIH public database

- Financial disclosure
- Pediatric Research Equity Act
- Pediatric exclusivity

Jan. 5, 2005 DDOP designated dasatinib a Fast Track product. This decision was based on preliminary data from Study CA180002 suggesting that dasatinib has activity in CML and Ph^+ ALL resistant or intolerant to imatinib.

July 7, 2005 A Pre-NDA meeting was held at which the following topics were discussed:

- The sponsor updated DDOP on the accrual of ongoing studies.
- The sponsor indicated that to demonstrate that its product is better than interferon-α, it plans to use published data on interferon-α post-chemotherapy rather than conducting a trial comparing the two treatments.
- The content of the Safety Update and Statistical Analysis Plans and the proposed format and content of the patient profiles, datasets, and narratives were reviewed.
- DDOP reminded the sponsor that a first-line treatment trial of dasatinib versus imatinib in CP-CML was strongly recommended to demonstrate clinical benefit. The sponsor stated that they planned to discuss this at another pre-NDA meeting in October 2005.

Oct. 27, 2005 A pre-NDA meeting was held at which the following topics were discussed:

- The sponsor presented an updated analyses of the six efficacy studies (CA180002, CA180005, CA180006, CA180013, CA180015, and CA180017), based on data collected through September 27, 2005. DDOP indicated that the studies appeared adequate for submission; however, fileability, product indications and the adequacy of the duration of follow-up would be review issues. The sponsor indicated that submitted safety and efficacy data would include a minimum of 6 months follow-up once the 120-day safety update is provided.
- The sponsor outlined three potential development strategies being considered for dasatinib in the first-line treatment of CML. These proposals, in general, all appeared acceptable. DDOP recommended that the protocols be submitted as Special Protocol Assessments in order to determine which of the three would be preferred.

Nov. 18, 2005 Orphan Drug designation was granted for the "Treatment of Philadelphia-positive acute lymphoblastic leukemia".

Nov. 28, 2005 Orphan Drug designation was granted for the "Treatment of chronic myelogenous leukemia".

Feb. 6, 2006 FDA facilitated expanded access to dasatinib through an Applicant-sponsored study entitled "Study of Dasatinib (BMS-354825) in Subjects with Chronic Myelogenous Leukemia with Accelerated or Myeloid or Lymphoid Blast Phase or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Who Are Resistant to or Intolerant of Imatinib Mesylate."

2.6 Other Relevant Background Information

None. There have been no regulatory actions in other countries.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

From a CMC perspective, the Sponsor has submitted sufficient and appropriate information to support the approval of the drug product. The physical and chemical characteristics, impurity profile, and stability for dasatinib drug substance and dasatinib tablets have been adequately demonstrated in this submission. The acceptance criteria are appropriate to ensure the identity, strength, quality, potency, and purity of both the drug substance and the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. In particular, the — assay provides an acceptable degree of separation of dasatinib from its impurities. Based on analysis of the stability data, the approved shelf life for SPRYCEL (dasatinib) Tablets, 20 mg, 50 mg, and 70 mg tablets is 24 months at room temperature.

3.2 Animal Pharmacology/Toxicology

3.2.1 Pharmacology/Toxicology Review: Nonclinical safety issues relevant to clinical use.

Toxicology studies were carried out in two species: rats and Cynomolgus monkeys. Those include: cardiovascular toxicities (e.g. hypertension, QT prolongation, and necrotic changes); hemorrhage (which was seen in multiple organs/tissues in the animals); electrolyte imbalance which can increase the potential for other toxicities (such as cardiac); renal toxicity; and gastrointestinal toxicities including ulceration. Of note, fibrosis and mineralization was observed in multiple organs/tissues in the animal studies: mineralization of the uterus, adrenal medulla, tubules and glomeruli of kidney, and vascular system (in heart, tongue, spleen, stomach, and pancreas), fibrosis in the heart, lung, spleen, kidney, and cecum. Fibrosis/ mineralization may impair the function of these organs/tissues.

All toxicities reported in the acute studies were also reported in the repeat-dose toxicology studies. Cardiac toxicities were more evident in the acute toxicity study conducted in rats than the repeat-dose studies.

Dasatinib was teratogenic at sub-therapeutic doses in both species tested.

3.2.2 Effects of dasatinib on platelet function.

Normal physiology

Platelet adhesion, activation, and aggregation at sites of vascular endothelial disruption are key events in thrombus formation. Platelet adhesion to collagen occurs both indirectly, via binding of the platelet glycoprotein (GP) Ib-V-IX receptor to circulating von Willebrand factor (vWF), which binds to exposed collagen, and directly, via interaction with platelet receptors GP VI and GP Ia/IIb. Platelet activation, initiated by exposed collagen and locally generated soluble agonists (thrombin, ADP, and thromboxane A_2), stimulates the release of platelet-derived growth factors, adhesion molecules and coagulation factors, activates adjacent platelets, and changes the GP IIb/IIIa receptor conformation. Platelet aggregation, mediated by fibrinogen and vWF via activated GP IIb/IIIa, leads to the formation of platelet-rich thrombi.

An important final common pathway in the signal transduction mechanisms through which platelet agonists promote adhesion, activation, and aggregation is the protein kinase C (PKC) family. Two tyrosine kinases Syk and Src physically interact with PKCα and regulate its activity.[41-44] Because dasatinib is a pan-Src inhibitor, the Applicant sponsored two studies, 0605P and 930008306 with primary objectives of evaluating the effects of dasatinib on hemostasis.

Study 0605P

0605P evaluated the effect of dasatinib on rat, monkey, and human platelet responses to ADP and collagen. Aggregation was measured by turbidometry. Shear-induced adhesion was measured by a cone and plate analyzer.[37] Whole blood coagulation was measured by thrombelastography.[38] The results of this study were as follows:

- Dasatinib at concentrations of 0.5 and 5 μg/mL inhibited ADP- and collagen-induced aggregation of human platelets by 99%. Inhibition of collagen-induced aggregation was irreversible while inhibition of the ADP response was partially reversed by increasing ADP exposure. Dasatinib at a concentration of 0.05 μg/mL had no observable effect.

- Dasatinib at 0.5 and 5 μg/mL inhibited shear-induced adhesion of human platelets 94% and 46%, respectively. No effect was detected at 0.05 μg/mL.

- Dasatinib at 5 μg/mL decreased tensile clot strength by 29% but did not affect the rate of clot formation. No effect was seen at 0.05 μg/mL.

The effect of dasatinib on platelet aggregation induced by ADP and collagen was greater than what would be expected by single pathway inhibitors such as clopidogrel or aspirin. Aspirin would inhibit the response to collagen with no effect on ADP, while clopidogrel would block ADP- but not collagen-induced aggregation. Neither aspirin nor clopidogrel would affect shear-induced platelet adhesion or clot strength. This profile is typical of broad-spectrum antiplatelet agents such as the GPIIb/IIIa antagonists eptifibatide and abciximab, which may cause an increased risk of bleeding.

Study 93000836

Study 930008306 evaluated the effects of orally and intravenously administered dasatinib on platelet aggregation function and bleeding times in rats. Reviewer's Table 1 summarizes the results.

Reviewer's Table 1: Study 93008306 experimental findings

Experiment	Findings
Oral administration/mesenteric bleeding time	
4 mg/kg	• Plasma concentration at 80 min = 32 ng/mL • Bleeding time at 60 min unaffected
8 mg/kg	• Plasma concentration at 80 min = 235 ng/mL • Bleeding time at 60 min unaffected, but site tended to re-bleed
Oral administration/cuticle bleeding time	
4 mg/kg	• Plasma concentration at 80 min = 14 ng/mL • Platelet aggregation unaffected • Bleeding time unaffected
8 mg/kg	• Plasma level at 80 min = 17 ng/mL • Platelet aggregation unaffected • Bleeding time unaffected
20 mg/kg	• Plasma concentration at 80 min = 382 ng/mL • ADP-induced platelet aggregation decreased 21% • Collagen-induced aggregation decreased 99% • Bleeding time increased 3-fold
IV administration/cuticle bleeding time	
630 µg/kg followed by 2.64 µg/kg/min	• Plasma concentration at 40 min = 69 ng/mL • Collagen-induced aggregation decreased 35% • Bleeding time unaffected
1260 µg/kg followed by 5.28 µg/kg/min	• Plasma concentration at 40 min = 154 ng/mL • Collagen-induced aggregation decreased 99% • Bleeding time increased 2.7-fold
2520 µg/kg followed by 10.56 µg/kg/min	• Plasma concentration at 40 min = 306 ng/mL • Completely blocked collagen-induced aggregation • Bleeding time increased 3.7-fold

Using a least-squares regression model, the Applicant found bleeding times to correlate significantly with plasma dasatinib concentrations ($t = 3.260$, $p = 0.004$). The slope estimate,

however, had a high standard error (1.512 + 0.464) and the proportion of variance in the bleeding time variable that was predicted by plasma concentration was relatively low (0.371).

Reviewer's comment: Both orally and intravenously administered dasatinib produced dose-dependent decreases in collagen-induced platelet aggregation and cuticle bleeding times in rats.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sources of clinical data are the trials conducted by the Sponsor. The Sponsor has been developing dasatinib for treatment of all phases of CML and Ph+ ALL in imatinib intolerant or imatinib-resistant patients by conducting one Phase 1 dose-ranging study and five Phase 2 studies. The Phase 1 study included patients with all phases of CML and Ph+ ALL; the five Phase 2 studies enrolled patients by phase of disease, as shown in Reviewer's Table 1 below (data from Sponsor's Table 1A, Clinical Summary of Efficacy).

The Sponsor allowed over-enrollment in the studies until additional studies could be initiated. Some of the over-enrolled subjects in the Phase 2 single-arm studies were included in the efficacy cohort as long as they had at least 6 months of follow-up.

The Sponsor emphasizes that the submitted results are from relatively short-term follow-ups. Subjects in phase 2 single-arm studies had a minimum 6 months of follow-up. Subjects in the randomized study had a minimum follow-up of 3 months. Subjects in the phase 1 study had a follow-up of up to 19 months. These follow-up periods were sufficient for evaluation of response rates, but not for durations of responses.

Four (4) of the 5 phase 2 studies were single-arm, because there are few treatment options for patients with chronic, accelerated, or blast phase CML or Ph+ ALL who are resistant to or intolerant of imatinib. In the fifth study, chronic phase imatinib-resistant CML patients were randomized to dasatinib or to higher than approved dose of imatinib.

The phase 1 study was designed to establish the MTD, define DLTs, and guide dosing in the phase 2 studies. However, as described below, efficacy results were the main determinant of dosing recommendation.

4.2 Tables of Clinical Studies

Reviewer's Table 2. List of Studies Supporting the Efficacy of Dasatinib in Subjects with CML or Ph+ ALL

Phase Study No.	Population	No. pf patients enrolled	No. of patients treated	Total enrolled [accrual target]
Phase 2, Two-arm, randomized CA 180017	Chronic phase CML [IM-R* only]	36	36	166 [150]
Phase 2, Single-arm CA 180013	Chronic phase CML [IM-R* or IM-I*]	198	186	424 [100]
Phase 2, Single-arm CA 180005	Accelerated phase CML [IM-R* or IM-I*]	120	107	197 [60]
Phase 2, Single-arm CA 180006	Myeloid blast phase CML [IM-R* or IM-I*]	80	74	124 [60]
Phase 2, Single-arm CA 180015	Ph+ ALL or lymphoid blast CML [IM-R* or IM-I*]	81	78	101 [[60]
Phase 1 CA 180002	Chronic, accelerated, or blast Phase CML and Ph+ ALL [IM-R* or IM-I*]	85	84	92 [60 – 100]

*IM-R is imatinib resistant; IM-I is imatinib intolerant.

4.3 Review Strategy

The review included:

- A survey of current literature on diagnosis, classification and treatment of CML, using standard textbooks, reviews, references submitted by the sponsor and publications listed in PubMed,
- Review of the minutes of all meetings with the Sponsor during the development of dasatinib,
- Review of the Sponsor's description of all the trials submitted with this NDA,
- Review of supporting tables and data listings of various aspects of the trials, especially cytogenetic and hematologic responses, for evaluation of Sponsor's claims,
- Review of datasets submitted as SAS transport files
- Review of patient narratives in selected cases,
- Consultations with Toxicology/Pharmacology, Clinical Pharmacology, Chemistry, and Statistics reviewers,
- Requests for additional information from the Sponsor,

- Review of Division of Scientific Integrity consultation,
- Formulation of conclusions and recommendations, and
- Evaluation of proposed labeling and revision of labeling.

4.4 Data Quality and Integrity

A request was made on March 10, 2006 to have Division of Scientific Investigations (DSI) inspect four clinical study sites. The sites were chosen on the basis of number of subjects enrolled in these trials. Two of the sites were in the United States and two were in Europe.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
— M.D. Univ. of Texas MD Anderson Cancer Center 1515 Holcombe Blvd Houston, TX 77030	CA180002 CA180005 CA180006 CA180013 CA180015	46 (CA180002) Phase 1 8 (CA180005) Phase 2 2 (CA180006) Phase 2 17 (CA180013) Phase 2 1 (CA180015) Phase 2	Chronic myeloid leukemia (chronic, accelerated, and blast phases) and Ph+ ALL.
Dr. Charles Sawyers UCLA 11-934 Factor Building 10833 Leconte Avenue Los Angeles, CA 90095	CA180002	38 (CA180002) Phase 1 2 (CA180005) 2 (CA180006) 2 (CA180013) 3 (CA180015)	Chronic myeloid leukemia (chronic, accelerated, and blast phases) and PH+ ALL.
Dr. Michele Baccarani Universita di Bologna Istituto di Ematologia Lorenzo E Ariosto Seragnoli Ospedale S. Orsola Via Massarenti 9 Bologna 40138 Italy	CA180005 CA180006 CA180013 CA180015	6 (CA180005) 5 (CA180006) 12 (CA180013) 3 (CA180015)	Chronic myeloid leukemia (chronic, accelerated, and blast phases) and Ph+ ALL.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Dr. Andreas Hochhaus Fakultaet Fuer Klinische Medizin Mannheim Theodor-Kutzer-Ufer 1-3 Mannheim 68163 Germany	CA180005 CA180006 CA180013 CA180015	4 (CA180005) 3 (CA180006) 28 (CA180013) 3 (CA180015)	Chronic myeloid leukemia (chronic, accelerated, and blast phases) and Ph+ ALL.

By June 7, 2006 the inspections were completed and a report was being drafted by Dr. Lauren Iacono-Connors. The inspections did not detect substantial issues that would invalidate the study results at any of the four sites.

4.5 Compliance with Good Clinical Practices

Informed consents met Federal and International standards. Protocol violations are described in the trials; they occurred in a minority of subjects. The trials appear to have been conducted in accordance with acceptable ethical standards.

The sponsor submitted a certification that debarred persons will not be involved in any trials, signed December 19, 2005.

4.6 Financial Disclosures

The Sponsor submitted financial disclosures statements by all investigators in all submitted studies. All investigators checked "No disclosable information."

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Dasatinib is available as 20 mg, 50 mg, and 70 mg immediate release film-coated tablets. Following oral administration, dasatinib is rapidly absorbed with peak concentrations occurring between 0.5 to 3 hours after dosing. The half-life of dasatinib is approximately 4-6 hours. Dasatinib exhibits linear pharmacokinetics, suggesting a dose-proportional increase in AUC, and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. There is no significant accumulation of dasatinib after multiple dosing for 8 days. Following a high-fat meal dasatinib C_{max} decreased by 24% and AUC increased by 14%. These results are not clinically relevant, and therefore dasatinib may be taken without regard to meals.

Twenty-one metabolites are present in systemic circulation, urine and/or feces following dasatinib administration. Metabolism occurs mainly by CYP3A4 activity. One inactive metabolite is formed by flavin-containing monooxygenase 3 (FMO3). Another inactive metabolite is formed by unknown oxidoreductases. The N-dealkylated metabolite M4 (BMS-582691) is the only active metabolite for dasatinib. Metabolite M4's AUC was only 7% of the parent drug, and therefore the contribution of M4 to the overall pharmacology of dasatinib is minor. After administration of 100 mg [^{14}C]-labeled dasatinib, over 85% of the total radioactivity was eliminated in the feces, suggesting minimal renal excretion of dasatinib. The parent drug accounted for 19.1% in the feces. Of the radioactivity recovered in urine, parent drug accounted for 0.12%. Plasma protein binding of dasatinib is 94%.

In vitro studies in human liver microsomes indicate that dasatinib was not an inducer but may be a weak inhibitor of CYP3A4. *In vivo*, concurrent administration of dasatinib with simvastatin (CYP3A4 substrate), caused an increase in the C_{max} and AUC of simvastatin by approximately 37% and 20% respectively, indicating that dasatinib is a weak inhibitor of CYP3A4. In addition, administration of dasatinib with rifampin (CYP3A4 inducer) resulted in significant decreases in dasatinib C_{max} and AUC by 81% and 82% respectively; therefore co-administration of dasatinib with CYP3A4 inducers should be avoided. A study looking at the effects of ketoconazole (CYP3A4 inhibitor) on dasatinib pharmacokinetics is ongoing.

Due to the pH dependant absorption of dasatinib, a study investigating the effect of gastric pH modulators with Maalox and famotidine was conducted. The results from this study indicate that administration of dasatinib with OTC antacids should be separated by at least 2 hours to avoid decreases in dasatinib exposure. The short term or long-term co-administration of dasatinib with H2 antagonists and potent proton-pump inhibitors is not recommended at this time due to significant decreases in dasatinib exposure (C_{max} by 63%; AUC_{0-12} by 60%) when administered concomitantly with the H2 antagonist famotidine.

5.2 Pharmacodynamics

Cytogenetic response is the best evidence of the pharmacodynamic effect of dasatinib (i.e. inhibition of proliferation of BCR-ABL-positive clones of hematopoietic cells). Please see the Efficacy section.

5.3 Exposure-Response Relationships

Exposure-response analyses were performed to characterize the relationships between trough levels of dasatinib and effectiveness (cytogenetic response, hematologic response) and trough levels of dasatinib and incidence of severe toxicity (grade 3/4) in CML and Ph+ ALL patients using logistic regression. Data from 5 phase 2 studies in chronic phase (CA180013 CA180017) and accelerated phase patients (CA180005, CA180006, CA180015) were included. Based on the limited data available, no significant correlation between C_{trough} of dasatinib and endpoints of effectiveness and safety could be discerned. Further data is being collected in ongoing Phase 2 studies, and a population PK model is being developed which could help identify a better relationship between exposure and effectiveness and safety.

5.4 Clinical Pharmacology Studies

The safety database for dasatinib includes 229 healthy adult volunteers enrolled in six clinical pharmacology studies. Those six studies are summarized in the following table.

Reviewer's Table 3: Healthy volunteer studies supporting this application

Study	n	Title
CA180-009	54	The Effect of a Light Fat and a High Fat Meal on the Pharmacokinetics of BMS-354825 in Healthy Subjects
CA180-016	75	A Formulation Comparability Study of BMS-354825 in Healthy Subjects
CA180-019	8	Mass Balance, Pharmacokinetics and Metabolism of [^{14}C]BMS-354825 in Healthy Male Subjects
CA180-020	24	A Phase 1 Study of the Effect of Gastric Acid pH Modulators on the Oral Bioavailability of BMS-354825 in Healthy Subjects
CA180-022	48	The Effects of BMS-354825 on the Pharmacokinetics of Simvastatin in Healthy Subjects
CA180-032	20	The Effects of Rifampin on the Oral Pharmacokinetics of BMS-354825 in Healthy Subjects

The median age of the 229 healthy volunteers was 33 years (range 18-50). The following table summarizes their genders and races.

Reviewer's Table 4: Gender and racial composition of healthy volunteers

Characteristic	N (%)
Gender	
Male	170 (74%)
Female	59 (26%)
Race	
Caucasian	151 (66%)
American Indian/Alaska native	2 (1%)
Asian	7 (3%)
Black/African-American	64 (28%)

Hispanic	1 (<1%)
Hispanic-black	3 (1%)
Spanish	1 (<1%)

Reviewer's comment: The largest demographic groups among the healthy volunteer population were males and Caucasians.

Safety information submitted for these six pharmacology studies were limited to CRFs containing AEs that led to early study termination and to datasets containing electrocardiographic conduction intervals. The following sections summarize the designs and principal findings of those 6 studies.

Study CA180-009

This was an open-label, randomized, three-period, three-treatment, crossover study designed to determine the effect of a light-fat and a high-fat meal on the PK dasatinib. All subjects were to receive single 100 mg oral doses of dasatinib in the fasting state, after a light-fat meal, and after a high-fat meal, and were randomized to 1 of 6 treatment sequences. The study concluded that food-related changes in dasatinib exposure should not be of clinical relevance, and that dasatinib can therefore be taken without regard to meals.

A total of 54 healthy volunteers were enrolled and treated. Six discontinued the study early because they either no longer met study inclusion criteria (2 subjects) or because of AEs (2 subjects). One subject experienced grade 2 urticaria, and one reported grade 1 cough, throat irritation, and pruritus. No QTc prolongation was detected (mean ΔQTcB 0.87 msec [95% CI: 2.23, -0.48]).

Reviewer's comment: No clinically significant safety signals appear to have emerged during Study CA180-009.

Study CA180-016

This was an open-label, randomized, 4-arm, single-dose study designed to compare the PK parameters, safety, and QTc effects of the 5 mg and 50 mg clinical forms, and the 20 mg and 50 mg commercial dosage forms of dasatinib. A total of 75 healthy volunteers were enrolled, and all subjects completed the protocol as designed. The study concluded that exposure was similar between the two formulations.

Because no subjects discontinued the study early, the Applicant submitted no AE reports. No QTc prolongation was detected (mean ΔQTcB -0.84 msec [95% CI: 0.10, -1.79]).

Reviewer's comment: No clinically significant safety signals appear to have emerged during Study CA180-009.

Study CA180-019

This was a single-dose, open-label study designed to characterize the mass balance, PK and metabolism of dasatinib in healthy adult male volunteers. All subjects received a single dose of 100 mg of [^{14}C] dasatinib oral solution containing 120 μCi of total radioactivity, followed by analysis of pooled blood, plasma, urine, and feces samples for radioactivity.

A total of 8 subjects were enrolled and treated. The study found dasatinib was eliminated primarily in feces. Six of 8 subjects reported AEs, none of which were serious or resulted in study discontinuation. Because no subjects discontinued the study early, the Applicant submitted no AE reports.

The mean change in QTcB was -1.31 msec (95% CI: 1.71, -4.33). No subject had a change in QTc greater than 60 msec or an absolute QTc value exceeding 450 msec.

Reviewer's comment: No clinically significant safety signals appear to have emerged during Study CA180-019.

Study CA180-020

This was an open-label, randomized, 3-period, 3-treatment, crossover study designed to study the effect of gastric pH on the oral bioavailability of dasatinib. All subjects received 100 mg oral dasatinib alone, after 40 mg oral famotidine, and after a 30 mL oral dose of an aluminum hydroxide/magnesium hydroxide antacid, randomized to 1 of 6 treatment sequences.

A total of 24 subjects were enrolled and received study treatment. The study concluded that dasatinib C_{max} and exposure are significantly reduced when administered following gastric antisecretory agents or within 2 hours of neutralizing antacids.

There were no deaths or SAEs during the study. All AEs were grade 1 or 2 except one grade 3 hyponatremia event (129 mEq/L). The most frequently reported treatment-emergent AE was headache. Thirteen subjects (54%) had a total of 20 headache events. Twelve events were grade 1 and 8 were grade 2. Ten headache events resolved within 1 day and the other two resolved within 4 days. Two subjects discontinued the study early – one because of a headache and one was lost to follow-up.

Twenty-one subjects had at least one laboratory abnormality at least one CTCAE grade higher on-treatment than pre-study. Those seen in ≥ 10% of subjects were prolonged prothrombin time (30%), hyponatremia (30%), anemia (21%), neutropenia (12%), and hypocalcemia (12%). Four subjects had at least one grade 2 laboratory abnormality – 1 neutropenia (1,300/mL), 1 hyponatremia (described above), 2 hyperkalemia (5.8 mEq and 5.9 mEq) and 1 hypophosphatemia (2.1 mEq).

The mean change in QTcB was -0.83 msec (95% CI: 1.57, -3.25). One subject had a 75 msec increase in QTcB (81 msec for QTcF). No QTc values exceeded 450 msec.

Reviewer's comment:

1. Eight subjects experienced asymptomatic grade 2-3 hyponatremia during the course of this study. The cause and significance of this observation is unclear.
2. No other significant safety signals appear to have emerged during Study CA180-020.

Study CA180-022

This was an open-label, randomized, 2-period, 2-treatment, crossover study designed to assess the effects of dasatinib on the pharmacokinetics of simvastatin. All subjects were to receive 80 mg oral simvastatin both alone and with 100 mg oral dasatinib, randomized to 1 of 6 treatment sequences.

A total of 48 healthy volunteers were enrolled and treated. The study concluded that co-administration of simvastatin with dasatinib increased the exposures to simvastatin and simvastatin acid by approximately 20% to 40% compared with simvastatin alone.

There were no deaths, SAEs, or discontinuations during the study. All AEs were grade 1 or 2 except for one grade 3 event of hypophosphatemia (1.9 mg/dL) that began on Day 9 (day of discharge) and for which no resolution date is available.

The most frequently reported treatment-emergent AE in both treatment groups was headache. Twenty-four subjects (50%) reported a total of 26 headache events. All headaches were grade 1. Eight (31%) required treatment with acetaminophen. Twenty four headache events resolved in less than 1 day, and the other two resolved within 2 and 3 days, respectively.

Seven grade 2 laboratory abnormalities AEs were identified – 3 hypophosphatemia (1.9 mg/dL, 2.4 mg/dL, and 2.4 mg/dL), 2 hyperkalemia (5.7 mEq/L and 5.9 mEq/L), 1 elevated creatine phosphokinase (527 U/L), and 1 anemia (Hb 9.6 g/dL). No patients reported muscle weakness.

The mean change in QTcB was +0.84 msec (95% CI: 4.11, -1.67). Two subjects had a total of 5 QTcB values exceeding 450 msec, 1 pre-study and 4 after simvastatin plus dasatinib administration (1 subject, 454 msec 4 hours post dosing; 1 subject, 458 msec, 466 msec, and 461 msec at 1, 4, and 24 hours post dosing, respectively). No absolute QTc value exceeded 500 msec.

Reviewer's comment:

1. Four of 48 (8%) patients experienced asymptomatic grade 2-3 hypophosphatemia during the course of this study. The cause and clinical significance of this observation is unclear.
2. No other significant safety signals appear to have emerged during Study CA180-032.

Study CA180-032

This was an open-label, single-sequence study evaluating the effects of 8 days of oral rifampin 600 mg once daily on the PK of single doses of imatinib. All subjects were to receive 100 mg

oral dasatinib in the morning on Days 1 and 9. Rifampin was administered in the evening from Day 2 through Day 9.

A total of 40 healthy volunteers were enrolled and treated. The study concluded that co-administration of rifampin with dasatinib reduced the C_{max} and AUC of dasatinib by 81% and 82% respectively. Rifampin also caused marked reductions in exposures of two primary active metabolites of dasatinib, BMS-582691 and BMS-606181.

The only AE experienced by more than 2 subjects was headache. All headache events resolved within one day and none required treatment. There were no SAEs or discontinuations of study therapy. Nine subjects (45%) had at least 1 higher on-treatment CTCAE Grade laboratory abnormality relative to pre-study values. Two subjects (10%) had on-treatment laboratory abnormalities recorded as AEs by pre-specified criteria (1 neutropenia, 1 leukopenia). No other laboratory abnormalities were considered clinically meaningful by the investigator.

The mean change in QTcB was +0.99 msec (95% CI: 3.65, -1.67). One subject had a QTcF value of 451 msec on Day 9, 0 hours, before dasatinib was co-administered with rifampin. No absolute change in QTc value exceeded 60 msec.

Reviewer's comment: No clinically significant safety signals appear to have emerged during Study CA180-032.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor's proposed indication is:
"SPRYCEL (dasatinib) is indicated for the treatment of adults with chronic, accelerated, or blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.
SPRYCEL is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy."

6.1.1 Methods

The results of all submitted trials were used in the efficacy review to support the proposed indications. The phase 1 dose-ranging study (CA180002) contains efficacy information for all phases of CML and for Ph+ ALL. Chronic phase CML studies (CP CML) (CA180017 and CA180013), the accelerated phase CML study (AP CML) (CA180005), the myeloid blast phase CML (MB CML) study (CA180006), and lymphoid blast CML (LB CML) and Ph+ ALL study (CA180015) address each category of patients.

6.1.2 General Discussion of Endpoints

Primary and secondary endpoints differed in the chronic phase studies (CA180017 and CA180013) and in the advanced phase studies (CA180005, CA180006, and CA180015), as shown below. The rationale for differences between early chronic CML response criteria and late-stage advanced CML and Ph+ ALL response criteria is that cytogenetic responses are difficult to evaluate in advanced subjects because of marrow fibrosis and poor marrow reserves.

Reviewer's Table 5. Primary and Secondary Endpoints in CP CML Studies (CA180017 and CA180013)

Endpoints	Cytogenetic parameters	Hematologic parameters
Primary endpoint	• Major cytogenetic response (MCyR)	-----
Secondary endpoints	• Durability of MCyR • Time to MCyR	• Complete hematologic response (CHR) • Durability of CHR • Time to CHR

Reviewer's Table 6. Primary and Secondary Endpoints in AP CML, MB CML, LB CML and Ph+ ALL Studies (CA180005, CA180006, and CA180015)

Endpoints	Cytogenetic parameters	Hematologic parameters
Primary endpoint	-----	• Overall hematologic response (OHR) • Major hematologic response (MaHR)
Secondary endpoints	• Major cytogenetic response (MCyR)	• Minor hematologic response (MiHR) • Durability of OHR and MaHR • Time to OHR and MaHR • Complete hematologic response (CHR) • No evidence of leukemia (NEL)

The above response parameters are defined as follows:

Hematologic Response Criteria:

1) Complete hematologic response (CHR) is defined in Sponsor's Table 3.5.2.1 below. Confirmed CHR was defined as CHR maintained for 4 weeks after first documented at ≥ Day 14. Failure to maintain CHR was defined by 2 or more consecutive records of non-response (an isolated single record of non-response in between two records of response was not considered a loss of response).
2) Major hematologic response (MaHR): meeting criteria for either CHR or NEL. MaHR was introduced (Amendment #3, August 26, 2005) because of the observation

that subjects achieving NEL have a durability of response similar to CHR but have some degree of neutropenia or thrombocytopenia due to a long history of previous treatments for CML or ALL and thus do not meet the full criteria of CHR.

3) No evidence of leukemia (NEL) is defined in Sponsor's Table below. In addition to persistent peripheral blood cytopenias, NEL is characterized by the absence of Ph+ metaphases on cytogenetic analysis.
4) Minor hematologic response (MiHR) is defined in Sponsor's Table below. MiHR, which is the return to chronic phase, was intended to separate this response from CHR and NEL as the duration of response was expected to be shorter for this cohort.
5) Overall hematologic response (OHR): best response of MaHR or MiHR.

Table 7. Hematologic Response Criteria

Table 3.5.2.1: Hematologic Response Criteria

Major Hematologic Response (MaHR)

Complete Hematologic Response (CHR)

1) White blood cell (WBC) ≤ institutional ULN
2) Absolute neutrophil count (ANC) ≥ 1000/mm^3
3) Platelets ≥ 100,000/mm^3
4) No blasts or promyelocytes in peripheral blood
5) Bone marrow blasts ≤5%
6) <5% myelocytes plus metamyelocytes in peripheral blood
7) Peripheral blood basophils < 20%
8) No extramedullary involvement (including no hepatomegaly or splenomegaly)

No Evidence of Leukemia (NEL)

1) WBC ≤ institutional ULN
2) Has at least 1 of the following 2 criteria:
   500/mm^3 ≤ ANC < 1,000/mm^3
   20,000/mm^3 ≤ platelets < 100,000/mm^3
3) No blasts or promyelocytes in peripheral blood
4) Bone marrow blasts ≤ 5%
5) <5% myelocytes plus metamyelocytes in peripheral blood
6) Peripheral blood basophils < 20%
7) No extramedullary involvement (including no hepatomegaly or splenomegaly)

Minor Hematologic Response (MiHR)

1) < 15% blasts in bone marrow and in peripheral blood
2) < 30% blasts plus promyelocytes in bone marrow and < 30% blasts plus promyelocytes in peripheral blood
3) < 20% basophils in peripheral blood
4) No extramedullary disease other than spleen and liver

Source: Appendix 1.10

Reviewer's note: MaHR (CHR + NEL) in the advanced disease setting (AP, MB, and LB/ Ph + ALL) is considered to be the primary endpoint "reasonably likely to predict clinical benefit" and therefore supportive of accelerated approval for dasatinib in CML. OHR, which includes MiHR, was evaluated as part of the review process but is considered less clinically significant than MaHR.

Cytogenetic Response: Major cytogenetic response (MCyR) rate was defined as the proportion of subjects with CCyR and/or PCyR, as defined in Reviewer's Table 8 below. Cytogenetic response was based on the prevalence of Ph+ metaphases in bone marrow. Ideally at least 20 metaphase cells were evaluated.

Reviewer's Table 8.Cytogenetic Response Criteria

	% Ph+ cells in metaphase in bone marrow
Complete cytogenetic response (CCyR)*	0%
Partial cytogenetic response (PCyR)*	> 0% - 35%
Minor cytogenetic response (MiCyR)	> 35% - 65%
Minimal cytogenetic response	> 65% - 95%
No cytogenetic response	> 95% - 100%

Disease Progression:

Progression was defined as the first occurrence of one of the following:

- Loss of CHR or of MCyR
- Increasing WBC
- Development of accelerated phase or blast phase CML

6.1.3 Study Design

All four single-arm Phase 2 studies and one 2-arm randomized Phase 2 study are multicenter, open-label studies. The Phase 1 study was carried out at two large cancer centers. The rationale for single-arm design is presented above.

Studies CA180013, CA180005, CA180006 and CA10015 were single-arm multi-center trials in patients with CP, AP, MB and combined LB and Ph^+ ALL. Patients enrolled on all these trials were either imatinib resistant or imatinib intolerant.

Imatinib resistance was defined as 1) progression of CP-CML on imatinib ≥ 400 mg/day, or 2) progression of AP-CML on imatinib ≥ 600 mg/day, or 3) MB- or LB-CML after at least 4 weeks of treatment with imatinib ≥ 600 mg/day.

Imatinib intolerance was defined as 1) imatinib-related toxicity that led to imatinib discontinuation, or 2) ability to tolerate imatinib at only ≤ 400 mg/day. The presence of specific genetic mutations that are thought to confer resistance was not required for enrollment in any of the studies.

The starting dose was 70 mg BID on all phase 2 studies, with dose reductions allowed for toxicity and dose escalation allowed for lack of response.

6.1.4 Efficacy Findings

6.1.4.1 Dose determination. Dasatinib dosing was explored for both Safety and Efficacy in dose-escalation study CA180002.

This was a phase 1 dasatinib dose-escalation study in the treatment of patients with all phases of CML (CP, AP, MB, LB) and with Ph+ ALL who have hematologic resistance to imatinib mesylate (Gleevec®). A total of 84 subjects were enrolled and had a minimum 3 months follow-up. Of these, 63 subjects with all phases of CML and Ph+ ALL were treated with escalating doses of dasatinib administered BID (CP CML cohorts were treated on a 5 days on and 2 days off every week schedule, except for one cohort of 3 subjects at the 70 mg BID dose who were treated by continuous dosing; AP CML, MB CML, and LB CML/Ph+ ALL cohorts were all treated by continuous dosing. Twenty-one (21) subjects with CP CML were treated with escalating doses of QD dasatinib administered on a 5 days on and 2 days off every week schedule. Intra-subject dose escalation occurred in some subjects started at lower doses as well as dose de-escalation in subjects started at higher doses. Reviewer's Table 9 shows the number of subjects in each disease group accrued at each BID dose level. Seven cohorts of 3 patients with CP CML each were treated with the following QD doses: 15 mg, 30 mg, 50 mg, 75 mg, 105 mg, 140 mg, and 180 mg.

Reviewer's Table 9. CA180002. Number of Subjects Accrued at Each BID Dose Level

Dose Level	CP CML N = 19	AP CML N = 11	MB CML N = 23	LB CML/Ph+ ALL, N = 10
25 mg BID	3	-	-	-
35 mg BID	7	-	-	1
50 mg BID	3	3	3	2
70 mg BID	6	3	11	3
90 mg BID	-	2	5	4
120 mg BID	-	3	4	-

The study is ongoing with 60% of subjects remaining on treatment (90% of CP CML patients, 64% of AP CML patients, 26% of MB CML patients, and 10% of LB CML/Ph$^+$ ALL patients) at the time of the report.

MTD and Recommended Phase 2 Dose: The criteria for determining MTD were not met in any of the treatment groups. Only 2 of 84 patients had adverse events that met the DLT criteria during the first four weeks of treatment: one had grade 4 thrombocytopenia in the 35 mg BID cohort of chronic phase CML patients, and one myeloid blast CML patient in the 120 mg BID cohort had grade 3 pleural effusion and grade 4 pericardial effusion. Hence, the recommended Phase 2 dose was based on primarily on efficacy rather than safety criteria.

Table 10 below illustrates the median dose required to achieve a cytogenetic or hematologic response for each disease category.

Reviewer's Table 10. CA180002. Median Dasatinib Doses at Which Responses Were Achieved – All Treated Subjects

Disease (N=number of patients)	Dose to achieve MCyR Median (range)	Dose to achieve CHR Median (range)
CP CML – QD dosing (N=21)	105 mg QD (30 mg QD – 180 mg QD)	105 mg QD (15 mg QD – 180 mg QD)
CP CML – BID dosing (N= 19)	60 mg BID (35 mg BID – 70 mg BID)	50 mg BID (25 mg BID – 70 mg BID)
AP CML – BID dosing (N=11)	90 mg BID (50 mg BID – 120 mg BID)	70 mg BID (50 mg BID – 120 mg BID)
MB CML – BID dosing (N= 23)	70 mg BID (50 mg BID – 90 mg BID)	70 mg BID (50 mg BID – 70 mg BID)
LB CML/Ph+ ALL – BID dosing (N=10)	70 mg BID (25 mg BID – 90 mg BID)	70 mg BID (70 mg BID – 90 mg BID)

On the basis of these findings, the Sponsor concluded that the recommended dasatinib dose for Phase 2 studies is 70 mg BID.

Reviewer's Comments on Dose Determination:

CP CML - Most of the MCyRs occurred in 50 mg BID (or 105 mg QD) and 70 mg BID cohorts, although MCyRs also occurred at low doses of 30 – 75 mg per day and at a high dose of 180 mg per day (Table 7). Thus, the optimal treatment dose appears to be about 100 – 140 mg/day. The median dose was 50 mg BID.

Reviewer's Table 11. CA180002. Dasatinib Doses at Which a MCyR Was Achieved in CP CML – All Treated Subjects

Total daily dose at which MCyR was achieved	Number of subjects with responses/Number treated	% with responses
15 mg	0/3	0%
30 mg	1/3	33%
50 mg	1/6	17%
70 - 75 mg	3/10	30%
100- 105 mg	6/6	100%
140 mg	6/9	67%
180 mg	1/3	33%
Total	18/40	45%

Advanced phases of CML and Ph+ ALL - The dose escalation scheme for these cohorts started with higher doses than in chronic phase CML. The results shown in Table 12 are

combined for all advanced phases of CML and Ph+ ALL. The highest response rates were with 50 mg BID and 70 mg BID.

Reviewer's Table 12. CA180002. Dasatinib Doses at Which a MaHR Was Achieved in AP, MB and LB CML, and Ph+ ALL – All Treated Subjects

Total daily dose at which MaHR was achieved	Number of subjects with responses/Number treated	% with responses
70 mg (35 mg BID)	0/1	0%
100 mg (50 mg BID)	3/8	38%
140 mg (70 mg BID)	5/17	29%
180 mg (90 mg BID)	2/11	18%
240 mg (120 mg BID)	1/7	14%
Total	11/44	25%

Based on the summaries of response data in Tables 7 and 8, a starting dose of 50 mg BID may be appropriate for chronic phase CML, advanced phases of CML and Ph+ ALL, with dose escalations as needed depending on response and toxicity.

Efficacy results in the dose escalation study are shown in Reviewer's Table 13 (BID dosing only in CP CML). MCyR was achieved in approximately 30% - 40% of subjects in all CML phase groups and in about 80% of subjects with lymphoid blast CML/Ph+ ALL. CHR was achieved in about 90% of CP CML patients and in much smaller percentages of patients with AP CML, MB CML, LB CML, and with Ph+ ALL.

Reviewer's Table 13. CA180002. Cytogenetic and Hematologic Response Rates – All Treated Subjects

Response	**CP CML BID dose N=19**	**AP CML N=11**	**MB CML N=23**	**LB CML/ Ph+ ALL N=10**	**Total N=63**
MCyR	8 (42%)	3 (27%)	8 (35%)	8 (80%)	27 (43%)
CHR	17 (89%)	5 (46%)	3 (13%)	3 (30%)	28 (44%)
MaHR	---	6 (55%)	7 (30%)	5 (50%)	

6.1.4.2 Demographic and Prior Treatment Characteristics

Demographic characteristics are summarized by phase of disease in Table 14. Prior treatment history and reason for discontinuation of imatinib are summarized by disease status in Table 15. The male: female ratio was nearly 1:1 in all populations except Ph^+ ALL, where it was nearly 2:1. Most patients on all studies were white. Patients with LB CML and Ph^+ ALL were slightly younger than patients in other studies. As might be expected, subjects with earlier stage disease had better performance status.

Most patients with CML had received prior interferon, and over half had received prior chemotherapy. Almost all of the patients with Ph^+ ALL had received prior chemotherapy, and many had also undergone bone marrow transplant. Length of prior imatinib therapy was longest in chronic and accelerated phase subjects and shortest among Ph^+ ALL subjects. Most patients had received imatinib doses of at least 400-600 mg/day and had discontinued imatinib due to disease progression.

Reviewer's Table 14. Baseline Demographics in the Four Single-Arm Phase 2 Studies

Baseline Parameter	**Chronic Phase N=186**	**Accelerated Phase N=107**	**Myeloid Blast N=74**	**Lymphoid Blast N=42**	**Ph^+ ALL N=36**
Gender (%)					
Male	46	51	55	52	64
Female	54	49	45	48	38
Age (years), median (range)	59 (24-79)	57 (23-86)	55 (21-71)	47 (19-72)	46 (15-85)
Race, (%)					
White	93	85	76	95	97
Black	4	5	10	2	0
Asian	2	10	15	2	3
ECOG performance status, (%)					
0	73	47	18	31	22
1	26	39	41	43	44
2	0	14	38	17	31
unknown	0	0	3	10	3

Table 15. Prior Therapy for CML and Ph^+ ALL

	Chronic Phase N=186	**Accelerated Phase N=107**	**Myeloid Blast N= 74**	**Lymphoid Blast N=42**	**Ph+ ALL N=36**
Median time from initial diagnosis (months)	64	91	49	28	20
Prior Therapy other than Imatinib					
Prior bone marrow transplant (%)	9	18	12	33	42
Prior chemotherapy (%)	43	67	66	79	92
Prior Interferon (%)	70	75	55	48	8
Prior hydroxyurea or anagrelide (%)	86	96	88	79	14
Length of Imatinib Therapy (%)					
< 1 year	20	8	15	48	44
1-3 years	26	24	38	29	53
> 3 years	54	68	47	24	3
Highest Imatinib Dose (%)					
>600 mg	52	59	49	52	47
400-600 mg	48	41	51	45	53
<400 mg	0	0	0	2	0

Best Hematologic Response to Imatinib (%)					
Complete	86	83	84	67	75
No Evidence of Leukemia	0	6	5	7	0
No Response	10	9	7	16	8
Unable to Determine	4	2	4	10	17
Best Cytogenetic Response to Imatinib (%)					
Complete	17	10	32	33	42
Partial	16	22	14	10	8
Other	66	65	53	57	50
Reason for Discontinuation of Imatinib					
Resistance	68	93	92	88	94
Intolerance	32	7	8	12	6

6.1.4.3 Duration of Treatment

The median duration of treatment is described by disease status in Table 16.

Reviewer's Table 16. Duration of Treatment

	Chronic Phase	**Accelerated Phase**	**Myeloid Blast**	**Lymphoid Blast**	**Ph $^+$ ALL**
Duration of therapy (months), median (range)	5.6 (0.03-8.3)	5.5 (0.2-10.1)	3.5 (0.03-9.2)	2.8 (0.1-6.4)	3.2 (0.2-8.1)

6.1.4.4 Efficacy Results – Single Arm Studies

A summary of cytogenetic and hematologic response data for all 5 studies is presented in Reviewer's Table 17. Forty-five percent of CP subjects achieved a MCyR, the primary endpoint in that population; ninety percent achieved CHR. In the advanced disease studies, MaHR and OHR were co-primary endpoints. MaHR was achieved in 59% of AP patients, 32% in MB, 31% in LBP and 42% in Ph$^+$ ALL. MCyR, a secondary endpoint, was achieved in about 30% of AP and MBP patients and in 50-58% of LBP and Ph+ ALL patients.

Reviewer's Table 17. Summary of Cytogenetic and Hematologic Responses – Percentages of Subjects with Responses in the Single-Arm Phase 2 Studies

	CA180013 Chronic (N = 186)	CA180005 Accelerated (N = 107)	CA180006 Myeloid Blast (N = 74)	CA180015 Lymphoid Blast (N = 42)	CA180015 Ph^+ ALL (N = 36)
Hematologic Response Rate (%)					
OHR (95% CI)	NA	80 (72 - 87)	53 (41 - 64)	36 (22 - 52)	47 (30 - 65)
MaHR (95% CI)	NA	59 (49 - 68)	32 (22 - 44)	31 (18 - 47)	42 (26- 59)
CHR (95% CI)	90 (85-94)	33 (24-42)	24 (15-36)	26 (3-17)	31 (16-48)
NEL (95% CI)	NA	26 (18-36)	8 (3-17)	5 (0.6-16)	11 (3.1-26)
MiHR (95% CI)	NA	21 (14 - 31)	20 (12 - 31)	5 (0.6 - 16)	6 (0.7 -19)
Cytogenetic Response Rate (%)					
MCyR (95% CI)	45 (37 -52)	31 (22-41)	30 (20 - 42)	50 (34 - 66)	58 (41 - 75)

The above response statistics remained the same after inclusion of patients in the dose escalation study (described above) and the randomized dasatinib vs. high dose imatinib study (described below) (Table 18).

Reviewer's Table 18. Summary of Cytogenetic and Hematologic Responses in All Studies – Percentages of Subjects with Responses – All Treated Subjects in Single Arm, Two-Arm, and Dose Finding Studies

Response	Chronic (N = 186)	Accelerated (N = 118)	Myeloid Blast (N = 97)	Lymphoid Blast/ Ph+ ALL (N = 88)
OHR	NA	74	56	38
MaHR	NA	54	32	34
CHR	91	34	22	28
MCyR	45	31	31	57

Time to response and duration of response:

- In CP CML, the median time to CHR was 15 days and to MCyR, 85 days.
- In AP CML, the median time to MaHR was 57 days.
- In MBP CML, the median time to MaHR was 57 days.
- In LBP CML, the median time to achieve MaHR was 33 days. In Ph^+ ALL, the median time to MaHR was 54 days.
- Most of cytogenetic and hematologic responses occurred during the first 3 months of treatment with dasatinib; few responses occurred during the second 3 months of follow-up.
- Median duration of MaHR was 3.7 months in LBP subjects (95% CI 2.8, upper limit not reached) with 6/13 responders progressing, and 4.8 months in Ph^+ ALL patients (95% CI 2.9 months, upper limit not reached) with 5/15 patients progressing per the FDA reviewer's analysis.
- Duration of responses could not be reliably estimated during this period of follow-up in subjects with CP, AP and MB disease as almost all subjects who achieved a response remained in response at the time of data cutoff.

Duration of response data for the four phase 2 single-arm trials are summarized with Kaplan-Meier plots in Figures 2-6 below.

Figure 2. Duration of CHR in CP CML (Sponsor's Figure 3.2A [6 month Efficacy Update]).

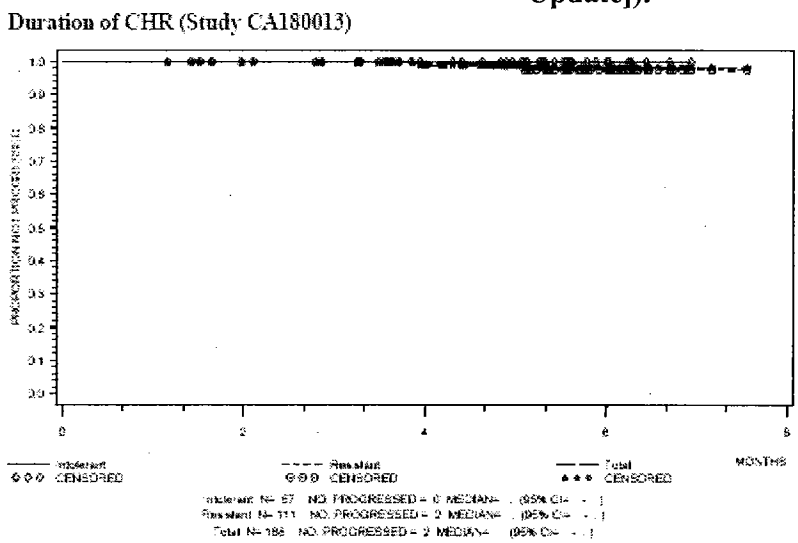


Figure 3. Duration of MaHR in AP CML (Sponsor's Figure 4.2A [6 month Efficacy Update]).

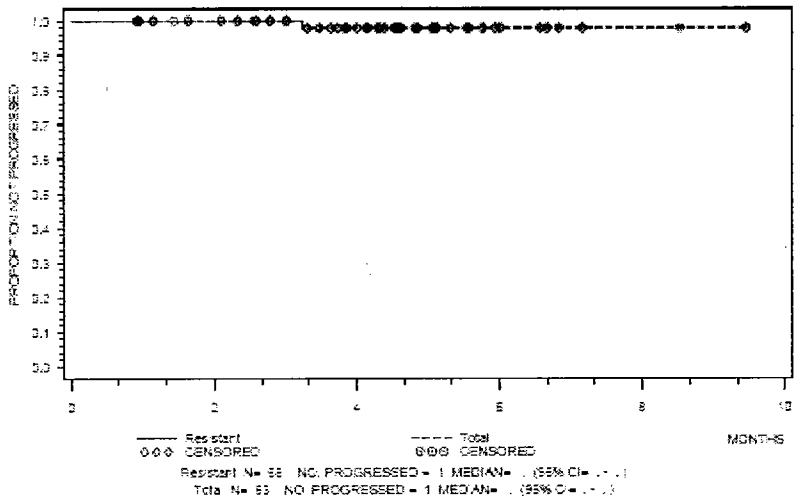


Figure 4. Duration of MaHR in MB CML (Sponsor's Figure 5.2A [6 month Efficacy Update]).

Duration of MaHR (Study CA180006)

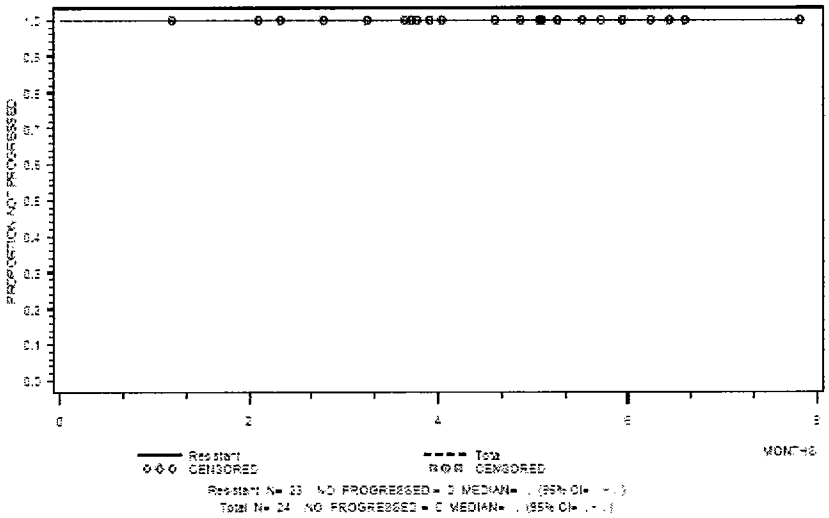


Figure 5. Duration of MaHR in LB CML (Sponsor's Figure 6.2A [6 month Efficacy Update]).

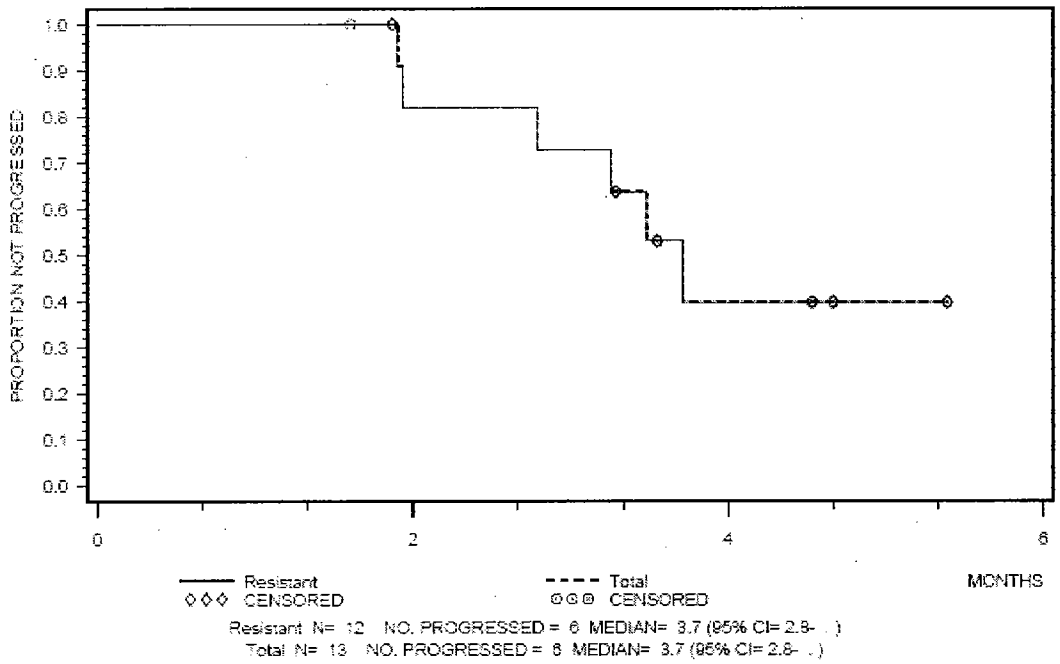
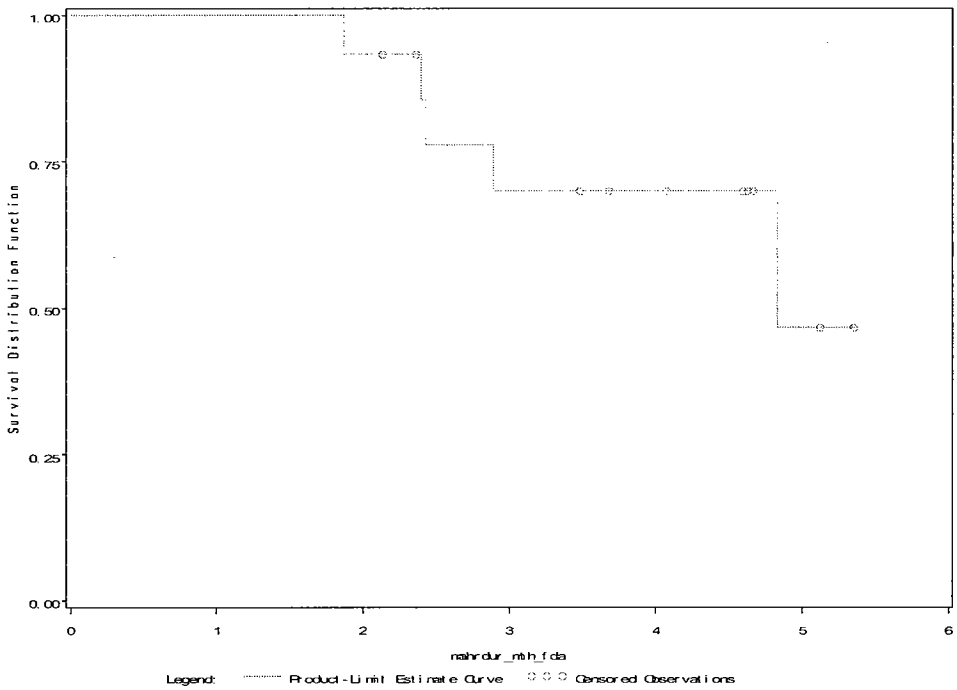


Figure 6. Duration of MaHR in Ph$^+$ ALL (FDA adjudicated data)



- Cytogenetic and hematologic responses among subjects with all phases of CML and with Ph+ ALL were associated with lower probability of disease progression, as shown in Reviewer's Table 19 below.
    - Among subjects with CP CML, none of the subjects who had a MCyR progressed and only 1 of 168 who had a CHR progressed. In contrast, 4 of 18 subjects (22%) who did not have a CHR progressed.
    - Among subjects with AP CML, only 1 of 28 (4%) subjects who had a MCyR progressed as compared to 8 subjects of 79 who did not have a MCyR and who progressed. Two percent (2%) of subjects with MaHR, 7% with OHR and 43% of subjects with no hematologic response progressed.
    - Among subjects with MB CML, 10% with MCyR and 38% of subjects with no cytogenetic response or in whom response could not be determined progressed. None of the subjects with MaHR progressed, 13% with any hematologic response, and 86% of subjects with no hematologic response progressed.
    - The relationship between disease progression and lack of response was also striking in LB CML and Ph+ ALL subjects. There was high rate of progression (43-48%) among both subject groups who had MCyR. The rate was about double (60% - 95%) in subjects who had no cytogenetic response. Similarly, the subjects without hematological response had about double the rate of disease progression or death of those with a hematologic response.

Reviewer's Table 19. Cytogenetic and Hematologic Responses and Subjects Who Progressed or Died - Percentages of Subjects who Progressed or Died during Minimum 6-Month Follow-up – All Treated Subjects

Disease phase	MCyR	No MCyR	MaHR	OHR	No Hematologic Response
CP CML, N = 186 (CA180013)	0/83 = 0%	5/103=5%	1/168=1%	---	4/18=22%
AP CML, N = 118 (CA180005)	1/28 = 4%	8/79=10%	1/63=2%	6/86=7%	9/21=43%
MB CML, N = 74 (CA180006)	2/21 = 10%	20/53=38%	0/24=0%	5/39=13%	30/35=86%
LB CML, N = 42 (CA180015)	10/21= 48%	20/21=95%	6/13=46%	7/15=47%	23/27=85%
Ph+ ALL, N = 36 (CA180015)	9/21 = 43%	9/15 = 60%	5/15=33%	7/17=41%	15/19=79%

6.1.4.5 Sub-Group analysis. Imatinib intolerant and imatinib-resistant populations.

Except for Study CA180013 which enrolled 27% patients with imatinib-intolerant CP CML, the enrollment of imatinib intolerant patients in all other studies was 10% or less. The imatinib intolerant population achieved higher cytogenetic and hematologic response rates than the imatinib-resistant CML population. The numbers of imatinib intolerant subjects were small in the other studies and appear insufficient to draw valid conclusions. This analysis is shown in Table 20 below.

Reviewer's Table 20. Responses in Imatinib Intolerant and Imatinib-Resistant Subjects in All Studies – All Treated Subjects

Disease phase	Intolerant N = 94		Resistant N = 457	
	MCyR	**CHR**	**MCyR**	**CHR**
Chronic	49/67 (73%)	65/67 (97%)	62/181 (34%)	161/181 (89%)
Accelerated	2/12 (17%)	3/12 (25%)	34/106 (32%)	37/106 (35%)
Myeloid Blast	2/7 (29%)	1/7 (14%)	28/90 (31%)	20/90 (22%)
Lymphoid Blast/ Ph+ ALL	6/8 (75%)	3/8 (38%)	44/80 (55%)	23/80 (29%)
Total (all phases)	59/94 (63%)	72/94 (77%)	168/457 (37%)	241/457 (53%)

6.1.4.6 Sub-Group Analyses. Efficacy responses based on age, race and gender.

Sponsor's analysis (Table 3.4) is presented in abbreviated form in Reviewer's Table 21. There were no response differences between subjects 65 years of age and younger and subjects over 65, and between females and males. No conclusions can be drawn about response rates in subjects of

races other than White, since they represented only about 10% of the total subject population (47 of 443).

Reviewer's Table 21. Primary Endpoint Results in Sub-Populations Analyzed According to Age, Race, and Gender

	CA180013 (CP CML) N = 186 MCyR 83/186 (45%)	CA180005 (AP CML) N = 107 OHR 85/107 (79%)	MaHR 58/107 (54%)
Age, years			
≤ 65	60/137 (44%)	66/81 (81%)	47/81 (58%)
>65	23/49 (47%)	20/26 (77%)	16/26 (62%)
Race			
White	77/173 (45%)	74/92 (80%)	57/92 (62%)
Black	3/8 (38%)	4/5 (80%)	2/5 (40%)
Asian	2/3 (67%)	8/10 (80%)	4/10 (40%)
Gender			
Female	44/100 (44%)	43/52 (83%)	36/52 (69%)
Male	39/86 (45%)	43/55 (78%)	27/55 (49%)

Reviewer's Table 21. (Continued)

	CA180006 (MB CML) N = 74 OHR 38/74 (51%)	MaHR 22/74(30%)	CA180015 (LB CML/Ph+ ALL) N = 78 OHR 30/78 (41%)	MaHR 27/78(36%)
Age, years				
≤ 65	30/58 (52%)	17/58 (29%)	28/68 (41%)	25/68 (37%)
>65	9/16 (56%)	7/16 (44%)	4/10 (40%)	3/10 (30%)
Race				
White	33/56 (59%)	22/56 (39%)	30/75 (40%)	27/75 (36%)
Black	3/7 (43%)	2/7 (29%)	1/1	0/1
Asian	3/11 (27%)	0/11	1/2	1/2
Gender				
Female	13/33 (39%)	9/33 (27%)	11/33 (33%)	10/33 (30%)
Male	26/41 (63%)	15/41 (37%)	21/45 (47%)	18/45 (40%)

6.1.4.7 Efficacy Results - Randomized, Two-Arm Study of Dasatinib vs. High-Dose Imatinib

Study CA180017 is a randomized, open-label, multi-center, non-comparative study of dasatinib 70 mg BID and imatinib 400 mg BID in patients with chronic phase CML and imatinib resistance defined as above. Patients were randomized in a 2:1 ratio to receive either dasatinib or imatinib administered continuously. Thirty-six patients with at least 12 weeks of follow-up are included in this report, 22 randomized to dasatinib and 14 to imatinib.

Dasatinib dose escalations were allowed for disease progression or lack of response, and dose reductions to manage drug toxicity. Imatinib dose escalation was not allowed; dose reduction to 600 mg daily was allowed. Crossover to alternative treatment was permitted for lack of response, disease progression or persistent intolerance. Cytogenetic assessment was to be performed every 12 weeks and at the time of crossover; hematologic assessment was performed weekly up to 12 weeks and biweekly thereafter. The primary efficacy endpoint was MCyR at 12 weeks.

Subjects were well balanced with respect to age, race, ECOG performance status, and prior therapy, except for bone marrow transplant (23% in the dasatinib arm and 0% in the imatinib arm). The male: female ratio was approximately 1:1 in the dasatinib group, while 93% of imatinib patients were female. (A fuller description of the trial is provided in the Appendix).

At the time of report, 11/14 imatinib arm subjects had crossed over to the dasatinib arm (because of intolerance [6 patients], failure to achieve MCyR [4 patients], and disease progression [1 patient]); 3/14 (21%) remain in the treatment arm. Twenty (20) of 22 patients in the dasatinib arm remain in the treatment arm (91%); 2/22 crossed over to the imatinib arm (one patient because of intolerance and one because of disease progression).

Preliminary efficacy results include a MCyR of 45% in the dasatinib arm and 21% in the imatinib arm (Reviewer's Table 22).

Reviewer's Table 22. CA180017. Cytogenetic Responses in Dasatinib and Imatinib Arms – All Randomized Subjects (Reviewer's Analysis)

Response	Dasatinib, N = 22	Imatinib, N = 14
MCyR (CCyR + PCyR)	10 (45%)	3 (21%)
---CCyR	7 (32%)	1 (7%)
---PCyR	3 (14%)	2 (14%)

6.1.5 Clinical Microbiology. N/A.

6.1.6 Efficacy Conclusions

1. Dasatinib treatment results in hematologic and cytogenetic responses in patients with all phases of CML and of Philadelphia chromosome-positive ALL who are resistant to or intolerant of imatinib mesylate, as shown by the results of one Phase 1 dose escalation study and of five Phase 2 studies in which 551 patients were enrolled and treated.

2. An effective starting dose of orally administered dasatinib is 70 mg BID. All Phase 2 trials were carried out using continuous 70 mg BID dasatinib dosing. Based on limited phase 1 data, lower doses of dasatinib, such as 50 mg BID, may be as effective as 70 mg BID and may result in less frequent dose interruptions and dose reductions.

3. Dasatinib treatment of patients with CP CML (N = 248) resulted in a 45% major cytogenetic response rate (MCyR), the primary efficacy endpoint, and a 91% complete hematologic response rate (CHR), a secondary efficacy endpoint. The median time to MCyR was 85 days, and to CHR, 16 days. Too few progression events have occurred to adequately estimate the duration of the responses. None of the subjects who achieved a MCyR had progressed during the minimum 6 month follow-up period.

4. Dasatinib treatment of patients with AP CML (N = 118) resulted in a 74% overall hematologic response (OHR) rate and a 54% major hematological response rate (MaHR, complete hematologic response + no evidence of leukemia), the primary efficacy endpoints, and a 31% MCyR, a secondary endpoint. The median time to MaHR was 57 days. The median duration of MaHR cannot be estimated at the minimum 6-month follow-up, as 98% of patients who achieved MaHR remained in MaHR.

5. Dasatinib treatment of patients with MB CML (N = 97) resulted in a 48% OHR and a 29% MaHR, the primary efficacy endpoints, and a 31% MCyR, a secondary endpoint. The median time to MaHR was 57 days. The median duration of MaHR cannot be estimated at the minimum 6-month follow-up, as 100% of patients with MaHR remained in MaHR.

6. Dasatinib treatment of patients with LB CML and patients with Ph^+ ALL (N = 88) resulted in an overall OHR of 38% and a MaHR of 34%, primary efficacy endpoints, and a 57% MCyR, a secondary endpoint. Among LB CML patients, the median time to MaHR was 35 days, and to OHR, 33 days. The median duration of MaHR was 3.7 months. At the 6-month minimum follow-up, 83% of patients had discontinued dasatinib, mainly because of disease progression and deaths. Among Ph^+ ALL patients, the median time to MaHR was 57 days, and to OHR, 35 days. The median duration of MaHR was 4.8 months. At the 6-month minimum follow-up, 67% of patients discontinued dasatinib, mainly because of disease progression, deaths, and dasatinib toxicity.

7. Most cytogenetic and hematologic responses occurred during the first 3 months of dasatinib treatment; few additional responses occurred during the second 3 months of treatment.

8. Cytogenetic and hematologic responses among subjects with all phases of CML and with Ph+ ALL were associated with lower incidence of disease progression.

9. There were no age- or gender-related response differences.

10. Imatinib intolerant subjects had overall higher cytogenetic and hematologic response rates than imatinib-resistant subjects in one Phase 2 study. The following subpopulations had approximately similar response rates: genetically resistant, clinically resistant, prior chemotherapy, prior interferon, imatinib > 600 mg/day, no prior CHR on imatinib, and no prior MCyR on imatinib.

11. In a small randomized trial of dasatinib vs. high-dose imatinib treatment in CP-CML, most of the patients in the imatinib arm crossed over to dasatinib because of lack of efficacy or intolerance.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This section reviews the safety findings in all studies involving patients with leukemias (CML of any stage and Ph + ALL). This included review of six clinical studies. Each represented a single stage of disease except for study 180002 (a phase 1 study done across all stages of CML and Ph + ALL) and study 180015, which included both CML lymphoid blast and Ph+ ALL. All studies were single-arm with the exception of a small, randomized study in chronic phase patients which enrolled 36 patients per arm and compared dasatinib to high dose (800 mg) imatinib. The overall safety population described by the sponsor included 511 patients as described in the following table from the sponsor's Summary of Clinical Safety (Table 1.1.1A, p. 20). A subset of patients from the phase 1 study was also included in this safety population.

Reviewer's Table 23. Dasatinib-Treated Subjects Included in the Safety Analysis—Sponsor's Table 1.1.1 A SCS p. 20

	Number of Subjects				
Study	Chronic CML	Accelerated CML	Myeloid Blast CML	Lymphoid Blast CML/Ph+ ALL	Total
CA180002	NA[a]	11	23	10	44
CA180005	0	107	0	0	107
CA180006	0	0	74	0	74
CA180013	186	0	0	0	186
CA180015	0	0	0	78	78
CA180017	22	0	0	0	22
Total	**208**	**118**	**97**	**88**	**511**

NA - Not applicable

[a] Additional subjects in CA180002 were enrolled with chronic CML: 19 subjects with BID dosing and 21 subjects with QD dosing. These data remain unpooled because of the different dosing regimens used with respect to the safety cohort.

Source: ISRs for CA180002, CA180005, CA180006, CA1800013, CA1800015, CA1800017

The reviewer's safety database included 489 patients with all phases of CML and Ph + ALL who were treated at a starting dose of 70 mg bid (the phase 2 dose). This included 214 patients with chronic phase CML, 110 patients with accelerated phase CML, 84 patients with myeloid blast

CML, and 81 patients with lymphoid blast CML or Ph+ ALL. Data analyzed were collected on 5 single-arm trials, and one small (n=36) randomized trial in chronic phase patients, where dasatinib was compared to high dose imatinib (800 mg). The patients treated at an initial dose of 70 mg bid are described in the sponsor's table 6.1 A (Table 25) below.

Table 24. Patients Treated at Initial Dose of 70 mg BID

Table 6.1A: Number of Subjects Accrued in Each Dose Cohort By Disease Group

Starting Dose	Chronic Phase CML		Accelerated Phase CML	Myeloid Blast Phase CML	Lymphoid Blast Phase CML / Ph+ ALL
	Once Daily	Twice Daily	Twice Daily	Twice Daily	Twice Daily
	N = 21	N = 19	N = 11	N = 23	N = 10
15 mg QD	3	-	-	-	-
30 mg QD	3	-	-	-	-
50 mg QD	3	-	-	-	-
75 mg QD	3	-	-	-	-
105 mg QD	3	-	-	-	-
140 mg QD	3	-	-	-	-
180 mg QD	3	-	-	-	-
25 mg BID	-	3	-	-	-
35 mg BID	-	7	-	-	1
50 mg BID	-	3	3	3	2
70 mg BID	-	6	3	11	3
90 mg BID	-	-	2	5	4
120 mg BID	-	-	3	4	-

The reviewer's safety population includes:

Chronic Phase: 186 patients from study 180013
+ 22 patients from study 180017 (all those initially treated with dasatinib)
+ 6 patients from study 180002 treated with 70 mg bid (see sponsor's table 6.1A)
---
214 patients

Accelerated Phase: 107 patients from study 180005
+ 3 patients from study 180002 treated with 70 mg bid
---
110 patients

Myeloid Blast Phase: 74 patients from study 180006
+10 patients from study 180002 treated with 70 mg bid
---
84 patients*

* only 10 patients at a starting dose of 70 mg bid were verified by the reviewer

Lymphoid Blast/ Ph + ALL: 78 patients from study 180015
+3 patients from study 180002 treated with 70 mg bid
---
81 patients

Patients on study 180017 who began on dasatinib and crossed over to imatinib were evaluated for adverse events up to the date of crossover. The two patients on this study who began on imatinib and crossed over to dasatinib are not considered in this safety population; both patients had very limited exposure to dasatinib prior to data cutoff.

Duration of Exposure:
Overall, most patients (57%) had a duration of 3-6 months of exposure to dasatinib, while 32% were treated for three months or less and 11% were treated for more than 6 months. Table 22 provides the duration of exposure by study. The longest durations of exposure were seen in the phase 1 study, where nearly one-third of patients received 6 months or more of dasatinib. This study is also the only study in which any patient received more than 12 months of exposure to dasatinib.

Reviewer's Table 25. Duration of Exposure by Study

Study	< 3 months	3-6 months	6-12 months	>12 months
CA 180002	41%	30%	27%	2%
CA 180005	21%	67%	12%	0%
CA 180006	43%	49%	8%	0%
CA 180013	26%	65%	9%	0%
CA 180015	55%	38%	6%	0%
CA 180017	14%	77%	9%	0%

7.1.1 Deaths

All deaths occurring on study or within 30 days of drug discontinuation were reviewed, regardless of the patient's starting dose of study drug. Deaths are described below according to disease phase. All deaths occurring in patients with CP or AP are summarized; narratives for deaths in patients with MB, LB, or Ph + ALL are included for those not solely related to disease progression or infection.

Chronic Phase CML:

The case report forms, adverse event tables and laboratory tables for all deaths occurring within 30 days of the last treatment date on studies CA180013 and CA180017 were reviewed. There were 3 deaths on study CA180013; no deaths were reported for patients on study CA180017.

Patient CA180013-19-13010 was a 65 year old male with chronic phase CML, who initiated dasatinib in February, 2005. He achieved a best response of CHR on 5/19/05 and disc treatment on June 30, 2005 with progression of disease to accelerated phase. He died later. Cause of death was listed as pneumonia and progressive disease.

Patient CA180013-47-13061 was a 45 year old woman with chronic phase CML wh dasatinib on 4/4/05. On she developed grade 3 weakness and bone pain an admitted to a local hospital for pain control. Other symptoms reported at that time headache (grade 1), nausea (grade 2), vomiting (grade 1), and lower extremity ede Per report of her husband, she died on — due to a CNS hemorrhage. Her pla prior to initiating dasatinib was 161; it had dropped to 70 by the first day of treatr on day 8 (4/11/05) and was 14 on the day she died. PT and PTT were normal.

Do you really think this date needs to come out?

Patient CA 180013-86-13151 was a 74 year old male who began dasatinib on 5/19/05. The dose was reduced to 50 mg bid on 6/1/05 due to asthenia and dyspnea (both recorded as grade 2, although asthenia described as "severe" and "profound"). The patient was hospitalized on — for asthenia; bone pain was also reported. The patient developed acute renal failure, elevated uric acid and hyperkalemia and died on — The reported cause of death was renal failure. Baseline creatinine was reported as elevated at 1.77, and was 2.18 on the last available date in the database (6/2/05). Additionally, the patient's total white blood cell count had dropped from 27.3 at screening to 10.2 on day 15, with a rise in serum uric acid from 3.1 to 13.1. Allopurinol was started on 6/3/05. Although there is no cause listed for renal failure, the laboratory data suggest the possibility of tumor lysis syndrome.

Two additional chronic phase CML patients died within 30 days of discontinuing drug on the phase 1 protocol CA10002. These patients were treated at doses other than 70 mg bid. The first, patient CA180002-2-203, was a 55 year old white male who began dasatinib in December, 2003 at a dose of 30 mg daily and discontinued on 4/9/04 due to disease progression. He died on — the cause of death was reported as progressive disease.

Patient CA180002-2-208 was a 57 year old male who began dasatinib in April 2004 and discontinued on August 2, 2004 due to disease progression. Cause of death was listed as intracranial hemorrhage with herniation that was attributed to disease progression. The platelet count was 78 at screening, remained under 100 throughout the study, and was 24 on the day dasatinib was discontinued. PT and PTT were normal at that time.

Accelerated Phase CML:

Four patients with accelerated phase CML died on treatment or within 30 days of discontinuation of treatment.

Patient CA18005-7-5105 was a 40 year old woman who began dasatinib on May 5, 2005. On she was hospitalized with grade 2 CHF. She was treated and improved by May 29 and was continued on dasatinib. A chest x-ray on July 25 showed marked increase in the left pleural effusion, which occupied early the entire left hemithorax. She discontinued therapy on , due to a pleural effusion and was hospitalized for evaluation and thoracentesis. Approximately 1.5 L of bloody fluid was removed; the fluid was negative for malignant cells and culture negative. The subject was subsequently hospitalized on due to elevated creatinine (grade 3), D-dimer (grade 2), confusion (grade 3), and hypercalcemia (grade 3). The subject reportedly died of disease progression with multi-organ system failure on

Patient CA18005-53-5051 was a 57 year old male who received dasatinib from March 31, 2005 to June 13, 2005. Past medical history included heavy smoking and chronic obstructive pulmonary disease. In May, 2005 he was diagnosed with Pneumocystis carinii pneumonia (PCP). Dasatinib treatment was interrupted and restarted at 50 mg bid on June 8 following "substantial recovery" from PCP. Despite this recovery, he continued to have large amounts of bronchial mucus. On June 13, he was found unresponsive. His death occurred on and was attributed to pneumonia, possibly PCP.

Patient CA18005-69-5030 was a 49-year-old Asian male with a history that included fungal pneumonia in Nov 2004 began dasatinib on March 12, 2005. Treatment was interrupted April 13 due to a low absolute neutrophil count (ANC) with bone marrow cellularity less than 10%. G-CSF was administered during this period of drug hold due to neutropenia. He was hospitalized on for fever (grade 1), tachycardia (grade 1) and exertional dyspnea. Laboratory values at that time showed a WBC of 1.16 x10^9/L with 99% neutrophils. Chest X-ray showed a multifocal pneumonia. Antibiotic therapy was initiated and G-CSF was continued. Leukemic relapse evidenced by WBC elevation led to resumption of dasatinib at a reduced dosage 100 mg total daily dose from June 8 to June 27, when it was interrupted again for gastrointestinal bleeding (grade 3). After a transient period of clinical improvement, the pneumonia worsened on June 30, with the subject developing sepsis and requiring intubation and mechanical ventilation for respiratory failure. A chest x-ray on confirmed worsening multifocal infiltration in both lungs with left pleural effusion. He died on due to pneumonia progression.

Patient CA18005-88-5059 was a 51-year-old white male with a history of blood cultures positive for Clostridium septicum 10 days prior to beginning dasatinib. He was treated as an outpatient with levofloxacin and metronidazole. Study therapy subsequently began on April 13, 2005. On the subject was admitted to the hospital with syncope, weakness and purpura. He was noted to be short of breath and tachycardic. He had recurrent syncope in the emergency room and became pulseless. Resuscitation efforts were not successful. Electrocardiograms were unremarkable for prolonged QT/QTc intervals. The cause of death per the investigator was 'shock'.

Myeloid Blast CML:

Twenty-two patient deaths occurred on treatment or within 30 days of discontinuation on study CA18006. The narratives for all deaths were reviewed. Summary information is presented here for those due to causes other than disease progression and infection.

Thirteen deaths were attributed to progressive disease. Three deaths were due to fatal bleeding and five were attributed to infection. One death was attributed to acute respiratory distress syndrome in conjunction with tumor lysis syndrome. An additional death was outside of the 30 day window, but was due to global cardiac insufficiency that was felt to be related to study drug; this death is also described here.

CA180006-4-6029 was a 38 year old woman who began treatment with dasatinib on March 22, 2005. She presented with a seizure on and was found to have a right frontal lobe hemorrhage. Platelet count at that time was 9. Follow-up CT and MRI on showed an increase in the size of the hemorrhage. The patient's death on was attributed to worsening hemorrhage.

CA180006-4-6057 was a 53 year-old white man who began dasatinib on April 29, 2005. He received platelet transfusions in June for a platelet count of 10. The subject was subsequently hospitalized on due to CNS hemorrhage. CT & MRI of the head showed multiple intracranial bleeds. Treatment included multiple platelet transfusions that did not stop the bleeding (no pre-transfusion platelet counts were provided). The subject died on

CA180006-19-6068, a 52-year-old white man, died due to intracerebral bleeding on the first day of dosing. Thirty minutes after receiving his first dose of dasatinib (70 mg), the patient fell out of bed and injured his head. Somnolence subsequently developed. Carotid compression tomography (CCT) showed intracerebral bleeding. Relevant laboratory values on included platelets 10.0/uL and INR 2.12. The patient died one hour later.

CA180006-69-6027, a 57-year-old man started dasatinib on March 25, 2005. On the patient was hospitalized with pulmonary infiltrates (grade 3). There was also a rapid increase in serum uric acid and creatinine consistent with tumor lysis syndrome (TLS). The patient was diagnosed with acute respiratory distress syndrome (ARDS), which was believed to be caused by tumor lysis syndrome. Treatment with dasatinib was interrupted. The subject was withdrawn from the study and transferred to hospice on Cause of death on was reported as ARDS. (Reviewer's note: TLS is not a well-recognized cause of ARDS. Review of the literature identified a case report *(Chest 1998; 113:550-52)* in which a patient with high grade lymphoma developed ARDS concurrent with TLS with no other identifiable predisposing factor for ARDS. This report postulated that the release of cytokines and other inflammatory mediators might have been responsible for the development of ARDS).

CA180006-43-6005 died 33 days after discontinuing dasatinib. His death is reported here because it was due to study drug toxicity (global cardiac dysfunction). The patient was a 28 year old man heavily pretreated for CML including prior anthracyclines who had baseline "minor"

mitral valve insufficiency and pericardial effusion but a normal baseline ejection fraction (50-55%). He began study drug on February 4, 2005. The patient was hospitalized for acute cholecystitis on and discontinued treatment at that time. He also was noted to have febrile pancytopenia. On his left ventricular ejection fraction was 45% (performed for unclear reasons) and he was described as having dilated cardiomyopathy and pulmonary arterial hypertension, both felt to be related to study drug. On his ejection fraction was 30%. He died due to global cardiac insufficiency and febrile pancytopenia on

On the phase 1 study CA18002, there were 7 patients in the myeloid blast phase of CML who died on study or within 30 days of discontinuing drug. Five of these deaths were attributed to disease progression, and one was attributed to metastatic solid tumor.

The remaining patient, CA180002-2-614 was a 55 year old female who began treatment with dasatinib at 90 mg twice daily on January 6, 2005. She discontinued treatment on January 28 due to hematologic toxicity and died on due to sepsis with multi-organ failure.

Lymphoid Blast/ALL:

There were 25 patient deaths on study in CA180015. Nine of these deaths were attributed solely to disease progression. An additional ten deaths were attributed to infectious causes including sepsis and pulmonary Aspergillosis.

CA1800015-13-15048, a 66-year-old female started dasatinib on Apr 16, 2005.
The subject was already hospitalized for an infection when, on she developed a pleural effusion and became hypoxic, requiring oxygen 24 hours per day. The pleural effusion required multiple thoracenteses. Dasatinib was interrupted. The subject had progressive hypoxia and progressive pleural effusion and died on .

CA1800015-15-15056, a 65-year-old female, began dasatinib on Apr 22, 2005. She was hospitalized twice with febrile neutropenia in . During the second episode, dasatinib was discontinued. She continued to be neutropenic and thrombocytopenic and suffered a fatal cerebral hemorrhage on Laboratory evaluation showed a white blood cell count (WBC):100, platelets: 1000/microliter, partial thromboplastin time (PTT): 1.29 (normal range 0.8-1.3) and international normalized ratio (INR):1.32 normal range 0.8-1.3).

CA1800015-70-15078, a 57-year-old male, began dasatinib on May 25, 2005; at the time of study start, his white blood cell count (WBC) was 443,100/mm3 and he complained of some shortness of breath. Hydroxyurea 2 g was given orally along with dasatinib and dexamethasone 40 mg was given daily for 4 days. The WBCs decreased to 19,000/mm3 on the 7th day with partial resolution of lymphadenopathy. However, the subject's dyspnea continued and an EKG showed sinus tachycardia. An echocardiography on June 7 showed thickening of pericardium with LVC plethora and constrictive pericarditis was suspected. Due to poor general condition and low platelet count, pericardiectomy was not performed. A thoracentesis was performed with only brief palliation of dyspnea. On , the subject became hypotensive and died. The cause of death was constrictive pericarditis.

CA1800015-7-15068, an 85-year-old female with past medical history including congestive heart failure, coronary artery disease, hypertension, gastric reflux, hypothyroidism, breast cancer 1993, and pneumonia/pleural effusion, began dasatinib on May 5, 2005. On May 23 (study day 19) she was noted to have grade 3 increase in % blasts in the peripheral blood and the dasatinib dose was increased to 100 mg BID on May 27 and allopurinol and hydroxyurea were initiated on May 31 (study day 27). On —, the subject presented to the clinic with increased shortness of breath and rising blood counts with increasing blasts and was hospitalized due to grade 3 dyspnea. A chest x-ray next day showed pleural effusions, and attempts at thoracentesis were unsuccessful. The dasatinib was discontinued on June 2 due to disease progression. The respiratory status deteriorated and she died on — due to respiratory failure.

CA180015-140-15069, a 26-year-old male, began dasatinib on May 4, 2005. He was hospitalized due to grade 4 neutropenic fever on —. The neutrophil count was 130 (baseline 200). He was treated with antibiotic therapy. The fever resolved; however, the subject had not yet fully recovered. A bone marrow aspiration and biopsy showed about 50% blasts (bone marrow blasts were 30% prior to the start of dasatinib). Administration of dasatinib was continued. The subject was re-admitted to the hospital with neutropenic fever on — —). He was treated with levofloxacin, voriconazole, sulfamethoxazole/trimethoprim, piperacillin sodium/tazobactam sodium and vancomycin. The subject's blood cultures grew Klebsiella pneumonae. A lung CT scan showed a left lower lobe infiltrate. On June 8, his white blood cell count was 0.9, hemoglobin was 9.1 and platelet count was 11. Administration of dasatinib was interrupted on June 9. A diagnosis of pneumonia with a Rhizomucor species of the lung was confirmed on June 19. His pneumonia and fever continued despite treatment. Fungal cultures were consistent with mucormycosis. The subject was treated with amphotericin B. He subsequently developed right lower lung infiltrates and cavitation. On July 21, he was restarted on dasatinib at 50 mg bid. He was admitted to the hospital on — with tachypnea and pulmonary bleeding. His platelet count was 6 x 10^9/L on August 31. The subject died on due to pulmonary hemorrhage.

On the phase 1 study CA180002, 3 patients with lymphoid blast CML or ALL died on study. Two of these deaths were attributed solely to disease progression, and one was attributed to progression complicated by Klebsiella sepsis. CA180002-2-609 was a 28 year old male who received 90 mg of dasatinib twice daily from November 18, 2004 until December 31, 2004, when he developed Klebsiella pneumonia and sepsis. Death on — was due to sepsis and multi-organ failure.

7.1.2 Other Serious Adverse Events

Serious adverse events (other than death) were defined as:

A serious adverse event (SAE) is any untoward medical occurrence at any dose that:

- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)

- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a cancer
- Is a congenital anomaly/birth defect
- Results in the development of drug dependency or drug abuse
- Is an important medical event (including pregnancy or overdose)

Serious Adverse Events in Individual Studies

CA 180002

There were 52 SAEs reported in sixteen patients (76%) in the 70 mg BID patient population.

The most common system organ classes (# of events) in which an SAE occurred were: general (11), infection (8), and neoplasms (7).

The most common events (# of patients) were: fever (5), pneumonia (3), disease progression (2), and neutropenic fever (2).

CA180013

There were 125 SAEs in 59 CP patients (32%) on study.

The most common system organ classes (# of events) in which an SAE occurred were: respiratory (25), cardiac (18), blood and lymphatic (17), general (15), infection and infestation (14), and gastrointestinal (12).

The most common events (# of patients) were: CHF/cardiac decompensation/ventricular failure (11), pyrexia (11), pleural effusion (10), dyspnea (9), pneumonia (8), thrombocytopenia (5).

CA180005

There were 166 SAEs in 58 AP patients (54%) on study.

The most common system organ classes (# of events) in which an SAE occurred were: blood and lymphatic (34), gastrointestinal (28), respiratory (23), infections and infestations (19), general (17) and investigations (14).

The most common events (# of patients) included gastrointestinal hemorrhage (14), thrombocytopenia (11), febrile neutropenia (10), pyrexia (10), pleural effusion (9), pneumonia (9), pulmonary infiltrates (4) and diarrhea (4). Other notable SAEs included right ventricular dysfunction (1) and congestive heart failure (1).

CA180006
One hundred and seventy-two SAEs were reported in 53 MB patients (72%).

The most common SOCs for these events included: respiratory (30), infections (24), neoplasms (20), blood and lymphatic (18), gastrointestinal (17) and general (14).

The most common events (# of patients) were: disease progression (20), fever (9), febrile neutropenia (6), pleural effusion (6), sepsis (5), GI bleed (5), pulmonary infiltrates (4), pneumonia (4), pneumonitis (4), anemia (4), pulmonary hypertension (3), congestive heart failure/cardiomyopathy (3) and thrombocytopenia (3).

CA180015

There were 185 SAEs in 60 LB/ Ph + ALL patients (77%) on study.

The most common system organ classes (# of events) in which an SAE occurred were: general (32), infection and infestation (27), blood and lymphatic (26), respiratory (21), neoplasms (18), gastrointestinal (17), nervous system (9) and investigations (9).

The most common events (# of patients) were: pyrexia (15), pneumonia (8), neutropenic fever (8), sepsis/septic shock (7), pleural effusion (6). Thrombocytopenia and anemia were each reported in 4 patients, and dyspnea, GI bleeding, vomiting and infectious colitis were reported as SAEs in 3 patients each.

CA180017

Seven SAEs in 4 dasatinib treated patients were reported. These included pulmonary hypertension, ventricular arrhythmia, rapid atrial fibrillation, pyrexia, bruise, dehydration and pneumonia.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 27 describes the number of patients who discontinued drug due to toxicity in the different disease populations.

Reviewer's Table 26. Drug Discontinuations due to Adverse Events in Patients Enrolled on Leukemia Studies (as reported by investigators)

Stage of Disease (n)	# patients (%)
Chronic Phase CML (214)	13 (6)
Accelerated Phase CML (110)	6 (6)
Myeloid Blast CML (84)	26 (31)
Lymphoid Blast CML/ Ph + ALL (81)	32 (40)

Discontinuations due to adverse events were more common in patients with more advanced stages of disease. This difference is largely due to the number of patients who discontinued due to disease progression in the advanced disease populations. Reasons for discontinuation in the different study populations are described below.

Among chronic phase patients enrolled in study 180013, reasons for drug discontinuation included CHF/pleural effusion (both grade 2), left ventricular systolic dysfunction (grade 3), increased QTc interval (grade 2), cough/interstitial lung changes/ pulmonary edema (grade 2), thrombocytopenia (grade 4), CNS bleeding (grade 5), renal failure (grade 5), pneumonia grade 3), neuropathy (grade 2), pyoderma gangrenosum (grade 3), Sweet's syndrome (grade 2), bone pain (grade 3), and erythema (grade 3)/prurititis (grade 2). The two subjects with grade 5 events were described under "deaths" in section 7.1.1.

In accelerated phase patients enrolled in study 180005, reasons for discontinuation due to adverse events included disease progression (2 patients), dyspnea (grade 3), acute pulmonary embolism (grade 4), GI hemorrhage (grade 3), and shock/sudden death. Excluding disease progression, four patients discontinued therapy due to AEs.

In myeloid blast patients enrolled on study 180006, 20 patients were reported as having discontinued therapy due to AEs. Ten of these discontinuations were for progressive disease (one associated with infection, another with anemia and thrombocytopenia). The remaining ten patients discontinued drug due to: CHF (grade 3) and pleural effusion (grade 2), myelitis (grade 4), fever (grade 2), "FEV" and dilated cardiomyopathy (both grade 3), transient ischemic attack (grade 3), pulmonary infiltrates (grade 5), pneumonitis (grade 5), urticaria (grade 3), and two patients for whom bone marrow/stem cell transplant was listed as the reason for discontinuation. Excluding disease progression and bone marrow transplant, eight patients discontinued therapy for AEs.

Among lymphoid blast CML and Ph + ALL patients on study 180015 who discontinued due to AEs, 15 were reportedly withdrawn due to disease progression. An additional patient was withdrawn due to "increased white blood cell count" which is also likely due to progressive disease. Other reasons for discontinuation included dyspnea, hypoxia/pleural effusion, pulmonary infiltrates, pulmonary hemorrhage, rash, fatigue, pre-transplant hospitalization, hemorrhagic shock, cranial nerve VII neuropathy, seizure, septic shock, and constrictive pericarditis. Eleven patients discontinued for adverse events other than progression or pre-transplant.

There were no discontinuations due to adverse events among CP patients enrolled on study 180017.

On the dose-escalation study in all stages of CML and in Ph + ALL patients, ten patients were reported to have discontinued due to AEs. All of these patients had MB CML (n=6) or LB/ Ph + ALL (n=4). Six of these patients were reported as due to progression with or without other AEs (including GI bleed and tumor lysis syndrome in one patient and Klebsiella sepsis in another).

Other reasons for discontinuation included Grade 4 neutropenia and thrombocytopenia, Grade 2 tumor fever, Grade 4 sepsis, and Grade 3 MI (without ST elevation)/ARDS.

Below is the reviewer's table (Table 28) of discontinuations due to adverse events in the safety population. This table excludes those patients in whom drug was discontinued due to progressive disease or pre-transplant hospitalization.

Reviewer's Table 27. Drug Discontinuations due to Adverse Events (other than progressive disease or pre-transplant) in Patients Enrolled on Leukemia Studies—FDA Review

Stage of Disease (n)	# patients (%)
Chronic Phase CML (214)	13 (6)
Accelerated Phase CML (110)	4 (4)
Myeloid Blast CML (84)	11 (13)
Lymphoid Blast CML/ Ph + ALL (81)	12 (15)

7.1.3.2 Adverse events associated with dropouts

The most common event listed among myeloid blast, lymphoid blast, and ALL patients as a reason for discontinuation was disease progression. Other reasons for dropouts in all stages of disease included cardiac events (CHF, left ventricular systolic dysfunction, dilated cardiomyopathy, MI, prolonged QTc, and atrial fibrillation), thromboembolic events (pulmonary embolism, TIA), severe infections (sepsis, pneumonia) and bleeding events (GI, CNS).

Other significant adverse events

Dasatinib Dose Adjustments:

Dosing interruptions and dose reductions due to toxicity were common on dasatinib studies. Hematologic toxicity was the most common reason for dose interruptions and dose reductions in chronic phase and accelerated phase patients; while non-hematologic toxicity was more commonly the reason for discontinuation in more advanced disease. The relative decrease in dose adjustments for hematologic toxicity in advanced disease patients likely reflects the higher incidence of severe hematologic abnormalities at baseline, and a higher tolerance for treatment related abnormalities in patients with more severe disease.
A small percentage of patients in all groups had dose adjustments for reasons other than toxicity (interruption for a procedure, dosing error, etc).

Reviewer's Table 28. Percent of Patients with Dose Adjustments

Disease Phase	Dose Reduction	Interruption
CP	50%	82%
AP	45%	73%
MB	35%	74%
LB/ Ph+ ALL	21%	68%

Cardiac events:

Patients with significant cardiac histories including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias or QTc prolongation were excluded from dasatinib trials.

Congestive heart failure/ventricular dysfunction

Twenty patients (4%) in the safety population had an event classified as CHF or ventricular dysfunction. Among the 20 subjects, twelve had some cardiac history: 8 subjects had a prior history of hypertension, two had a history of valve disorders, two had pericardial effusions, one had an MI approximately 9 years prior, one had a history of CHF, one had a cardiomyopathy and one had a history of TIA. . The table below summarizes these events by subject ID, age, investigator's term and grade (NCI CTCAE version 3.0).

Reviewer's Table 29. Cardiac Failure Events on Dasatinib Leukemia Studies

Subject ID	Age	Investigator Term	Grade
CA180005-27-5107	48	Right ventricular dysfunction	3
CA180005-39-5056	56	Cardiac failure	2
CA180005-7-5105	40	Congestive heart failure	2
CA180006-10-6046	70	Congestive heart failure	3
CA180006-103-6053	63	Left ventricular systolic dysfunction	3
CA180006-43-6005	28	Dilated myocardiopathy*	3
CA180006-9-6076	68	Congestive heart failure	3
CA180013-11-13186	64	Left ventricular systolic dysfunction	3
CA180013-22-13011	65	Cardiac decompensation	3
CA180013-22-13014	60	Pleural effusion due to congestive heart failure	4
CA180013-22-13031	63	Symptomatic congestive heart failure	3
CA180013-22-13058	68	Cardiac decompensation	2
CA180013-22-13064	70	Cardiac decompensation	2
CA180013-22-13122	56	Bilateral heart failure	2
CA180013-24-13136	53	Congestive heart failure	2
CA180013-43-13051	66	Left ventricular systolic dysfunction	2
CA180013-85-13175	63	Left ventricular diastolic dysfunction	3
CA180013-88-13146	73	Cardiac general (CHF)	3

CA180013-88-13196	79	Symptomatic congestive heart failure	3
CA 180015-47-15008	47	Congestive heart failure	3

* this event is recorded here because the patient subsequently died of global cardiac insufficiency

Median time from start of study drug to onset of ventricular dysfunction/cardiac failure in study patients was 19 days (range 3-104).

Among the 20 events, 14 were reported as SAEs. 4 events led to drug discontinuation, 9 led to drug interruption, 1 led to dose reduction; no action was taken with respect to dose for 6 events. Twelve patients with cardiac failure events had chronic phase CML, 3 were in accelerated phase, 4 in myeloid blast phase and 1 patient had lymphoid blast/ Ph+ ALL.

One event led to death (subject 180006-43-6005). His death is also reported under section 7.1.1. This patient was a 28 year old male with myeloid blast CML with a past history of anthracyclines exposure who began dasatinib February 1, 2005 and discontinued the drug on February 21, 2005. He was reported to have developed dilated cardiomyopathy which was "probably" drug related. His death occurred on —, the cause of death was reported as global cardiac insufficiency and febrile pancytopenia.

An additional death in which cardiac failure may have had a role was patient CA180013-11-13186. An update on the event was provided in the 120 day safety update. This patient, who had a history of hypertension and CHF, experienced a myocardial infarction on study day 8, associated with grade 3 ventricular dysfunction. She remained on study for 116 days following the ventricular dysfunction event. Approximately 7 weeks after discontinuing dasatinib she began receiving another experimental bcr-abl inhibitor. Within days (one to four—the timeline is unclear) she developed tachycardia and dyspnea. This had a fatal outcome. Cause of death was listed as arrhythmia and cardiovascular arrest.

QT prolongation
Nine patients had 10 events of QT prolongation reported as adverse events. Worst CTCAE grade was 4 in one patient, grade 3 in five patients, and grade 1/2 in the remainder. The drug was discontinued in one patient, interrupted in four patients and dose reduced in one patient; no action was taken with respect to study drug in 3 patients (all with grade 1 events). A summary of these and possibly related events including ventricular arrhythmias and syncope are described in the sponsor's table below (Integrated ECG summary p. 55).

Table 30. QT Prolongation and Related Adverse Events

System Organ Class	MedDRA Preferred Term	Number of Subjects with:		
		SAEs	Non-Serious ADRs	Unrelated Non-Serious AEs
Cardiac Disorders				
	ventricular arrhythmia	1		
	ventricular tachycardia	1		
	arrhythmia		1	3
General Disorders and Administrative Site Conditions				
	death or sudden death	3		
Investigations				
	electrocardiogram QT corrected interval prolonged	3	5	1
	electrocardiogram change		1	
Nervous System Disorders				
	syncope	3	1	7
	convulsion	3		5

Source: Dasatinib Clinical Safety Summary[4] Appendix 2 (SAEs) and Table S.B2, S.C2, S.D2, and S.E2 (ADRs)

Narratives for events summarized in the table were reviewed. Two of the three "sudden deaths" are described in section 7.1.1 and do not appear to be related to QTc prolongation. The third occurred more than 30 days after drug discontinuation and occurred at another hospital; details were unavailable.

Overall, 9 patients in the safety population (1.8%) had QTc prolongation reported as an adverse event.

Three patients with grade 3 QTc prolongation were reported as SAEs.

1. One subject (CA180015-4-15057), a 56-year-old male, had an ECG machine calculated QTcB value of 537 msec following the first dose of dasatinib 70 mg. This resolved the same day. His medication was interrupted 3 days later for this reason. Upon resuming treatment a week later at a reduced dose of 50 mg, the Investigator reported a second SAE of QTc prolongation (based on an ECG machine-calculated QTcB value of 606 msec); study drug was again held and the QTc prolongation again resolved later the same day. Treatment was restarted 4 days later at 40 mg BID, and no further events of QTc prolongation were reported. Subsequent over-reads of all ECGs by the central ECG laboratory found no QTcB values >498 msec.

2. A second subject (CA180006-2-6007), a 56-year-old male, had a SAE of prolonged QTc. After 8 days of treatment with dasatinib 70 mg BID, the ECG machine-calculated QTcB was 60

msec greater than baseline, and several measurements exceeded 500 msec. Dasatinib was held. The central ECG laboratory confirmed that QTcF ranged between 489 and 541 msec on that day, and QTcB between 497 and 563 msec. His baseline QTcF values had all been <406 msec (screening, 448 msec); his baseline QTcB ranged between 404-428 msec (screening, 466 msec). The day after interrupting treatment, the first QTcF was 518 msec, followed by values between 491 to 502 msec. Dasatinib was restarted 2 days later at a reduced dose of 50 mg BID. There were two QTcB values of 521 and 516 msec after the first dose of 50 mg. Repeat ECGs revealed no further QTcF prolongation (450 and 426 msec at ~2 and 3 weeks, respectively).

3. A third subject (CA180005-4-5047), a 57-year-old Asian female, experienced SAEs of rash, fever and a prolonged QTc after her first dose of dasatinib 70 mg.
Based on the ECG machine-read values, her QTcB was prolonged to 491 msec (61 msec longer than baseline) at 6 hours, but resolved within 4 hours. Dasatinib was not interrupted. ECGs on Day 8 showed no QTcF values >464 msec. Dasatinib was discontinued at Day 18 due to the SAE of generalized rash that appeared at about the same time. The subject subsequently died of disease progression.

Narratives for three additional patients with grade 3/4 events of QTc prolongation but not reported as SAEs are below.

4. Subject CA180006-10-6046 was a 70-year-old female who was reported to have Grade 4 QTc prolongation after 3 days of dasatinib treatment which resolved 2 days later. The Investigator considered the event to be probably related to study medication. The subject had a SAE of CHF 6 days after the resolution of the QTc prolongation event. QTc intervals are not available at the time of the QTc prolongation ADR.
The pre-dose (Day -1) QTc intervals were all <453 msec and the post dose Day 1 QTc intervals did not exceed 461 msec. On Day 12, near the time of the CHF SAE, the QTc interval did not exceed 463 msec. ECGs taken over the next 4 months showed normal QTc intervals.

5. Subject CA180015-56-15066 was reported to have Grade 3 QTc prolongation which resulted in dose interruption after 29 days of dasatinib treatment. The QT/QTcB/QTcF intervals for this 35-year-old female subject at the time of the event were 472/568/534 msec, respectively. The event was reported as lasting 6 days although the QTc intervals 2 days later were all <410 msec. The subject also had an isolated ECG abnormality of "abnormal U waves" which was associated with normal QTc intervals.

6. Subject CA180013-1-13018, a 78 year old male, was reported to have Grade 3 QTc prolongation after 8 days of treatment with dasatinib and resulted in dose interruption.
The QT/QTcB/QTcF intervals at the time of the event were 472/499/490 msec, respectively, and were accompanied by an ECG abnormality of RBBB with a QRS interval of 138 msec. The event resolved after 1 day and was considered as possibly related to study medication by the Investigator. Seven days later the subject had an ECG abnormality of prolonged QTc (intervals of 430/503/477 msec) that were again present in the setting of a RBBB. These abnormalities were not considered AEs.

Two additional events were examined for a possible relationship to QT prolongation and are described below.

The subject with an SAE of ventricular arrhythmia (180017-31-17003) was a 42 year old male with a prior history of diabetes and hypertension. He received a protocol exception to participate because his baseline QTc was > 450 msec on serial ECGs. As a precaution, he was initiated on a dose of 50 mg bid, and escalated to 70 mg bid one week later. He complained of chest tightness, palpitations and shortness of breath in April, these symptoms had been experienced by the patient prior to starting study drug. Echocardiogram at that time (4/15/05) was unremarkable except for increased pulmonary arterial pressure. Holter monitor on 4/26/05 showed a 5 beat run of ventricular tachycardia. Drug was interrupted on 4/29/05. Holter monitoring on 5/9/05 did not show any evidence of ventricular tachycardia. Drug was resumed without further arrthymic events.

One subject (CA180002-1-101) had a reported ECG abnormality of "ventricular tachycardia"; however, review of this ECG tracing by BMS found only normal sinus rhythm. The central ECG laboratory subsequently confirmed that this was a data entry error.

ECG analyses were performed by a central laboratory; the results of these analyses are described in section 7.1.9.

Fluid retention events:

Pleural effusion
Pleural effusion was reported in 120 patients (25%) across all studies. The worst grade reported was grade 1/2 in 93 patients, grade 3 in 24 patients, grade 4 in 2 patients, and grade 5 (fatal) in one patient. Forty-eight actions were taken with study drug for 176 events. The drug was interrupted in 43, discontinued in three cases and reduced in one. In one case, the dose was increased due to disease progression).

Pericardial effusion
Pericardial effusion was reported in 20 patients (4%). Worst grade reported was grade 1 in 16 patients, grade 3 in 2 patients and grade 4 in 2 patients. The event resulted in drug interruption in 3 patients. Eight patients had myeloid blast disease, 2 had lymphoid blast or Ph + ALL, 5 had accelerated phase CML and 7 had chronic phase CML.

Bleeding Events:

In addition to the disease-related risk of bleeding events in CML patients, a possible drug-related mechanism of platelet dysfunction was identified in nonclinical studies. *In vitro* data demonstrated that dasatinib inhibits collagen-induced platelet aggregation in human, cynomolgus monkey, and rat platelet-rich plasma, and that dasatinib reduced human whole blood clot strength.

Bleeding events of any type occurred in 34% of patients. Grade 3/4 bleeding events occurred in 10% of patients. Grade 5 (fatal) bleeding events occurred in 6 patients. Five of these were CNS

hemorrhages and one was a pulmonary hemorrhage. Epistaxis was the most common single event, occurring in 11% of patients. Gastrointestinal bleeding events occurred in 10% of dasatinib-treated patients; grade 3/4 events occurred in 6%. Other sites included gingival, conjunctival, CNS, vaginal, urinary tract, eye, and respiratory tract.

CNS Hemorrhage

Six patients experienced CNS hemorrhage while receiving dasatinib. Five of these patients had fatal CNS hemorrhages. These events are summarized in Reviewer's Table 28.

Reviewer's Table 31. Bleeding Events

Bleeding Event	Grade	Disease Phase	Platelet Count	Additional Information
Intracranial hemorrhage	5	Chronic	14,000	
Cerebral hemorrhage	5	Lymphoid Blast	1,000	
Cerebral hemorrhage	5	Myeloid Blast	9,000	
Intracranial hemorrhage	5	Myeloid Blast	21,000 (3d prior)	Platelet count 10,000 at start of study
Cerebral hemorrhage	5	Myeloid Blast	10,000	Pre-treatment platelets 14,000; Head injury d/t fall following first dasatinib dose
Subdural hematoma	3	Ph + ALL	56,000	Resolved after surgical tx; pt. resumed dasatinib

7.1.4 Other Search Strategies

No special search strategies were employed in the course of this review.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Safety and tolerability were assessed through collection of spontaneously reported AEs, measurement of vital signs, and routine laboratory testing at each visit. Investigators were asked not to report hematologic abnormalities as adverse events as it was felt that a more accurate assessment of hematologic abnormalities could be obtained from the laboratory data. These events were reported inconsistently as AEs in different clinical trials.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded verbatim from the CRF (AECRF), by lower level term and by preferred term. They were also tabulated by system organ class (SOC). Severity of on-study

AEs was graded by the investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3 grading system. The investigator's adverse event terms were coded and grouped by preferred term and system organ class using the MedDRA dictionary (version 8.0) and were summarized by any grade, Grade 3 to 4, and Grade 5 (death). In general, the reviewer found that events were appropriately coded to a preferred term.

7.1.5.3 Incidence of common adverse events

Across the development program, the most common adverse events were gastrointestinal (diarrhea, nausea, abdominal pain, and vomiting), constitutional symptoms (pyrexia, headache, fatigue, asthenia, anorexia and weight loss), fluid retention events such as peripheral edema and pleural effusion, and bleeding were also commonly reported.

As expected, some events were more commonly reported in more advanced disease. Febrile neutropenia was reported in 10% of the overall population, < 10% of patients in chronic phase and in 27% of patients with LB or Ph + ALL. Petechiae and bleeding events were also more commonly reported in advanced disease, where patients were more likely to have severe thrombocytopenia.

Common adverse event tables

Common adverse event tables are presented by stage of disease and in the overall safety population.

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ON ORIGINAL

Chronic Phase

Reviewer's Table 32. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Subjects in CP CML

CP CML n=214		
Adverse Event, n (%)	**Any Grade**	**Grade 3/4**
Any	210 (98)	109 (51)
Headache	87 (41)	4 (2)
Fatigue	75 (35)	4 (2)
Diarrhea	72 (34)	5 (2)
Dyspnea	64 (30)	7 (3)
Rash	63 (29)	2 (1)
Nausea	56 (26)	2 (1)
Pyrexia	48 (22)	4 (2)
Asthenia	45 (21)	3 (1)
Thrombocytopenia	42 (20)	39 (18)
Edema, peripheral	39 (18)	0 (0)
Cough	38 (18)	1 (1)
Bleeding (any site)	36 (17)	4 (2)
Abdominal pain	33 (15)	1 (1)
Pain in extremity	28 (13)	2 (1)
Vomiting	27 (13)	2 (1)
Bone pain	25 (12)	2 (1)
Pleural Effusion	24 (11)	5 (2)
Neutropenia	22 (10)	22 (10)
Dizziness	21 (10)	1 (1)

Accelerated Phase

Reviewer's Table 33. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Subjects in AP CML

AP CML n=110		
Adverse Event, n (%)	**Any Grade**	**Grade 3/4**
Any	110 (100)	76 (69)
Diarrhea	69 (63)	11 (10)
Pyrexia	50 (45)	7 (6)
Headache	47 (43)	2 (2)
Bleeding (any site)	42 (38)	10 (9)
Nausea	37 (34)	0 (0)
Fatigue	36 (33)	4 (4)
Abdominal pain	35 (32)	1 (1)
Rash	34 (31)	2 (2)
Edema, peripheral	34 (31)	0 (0)
Dyspnea	33 (30)	8 (7)
Cough	30 (27)	2 (2)
Asthenia	27 (25)	4 (4)
Vomiting	26 (24)	1 (1)
Arthralgia	23 (21)	0 (0)
Pleural Effusion	22 (20)	3 (3)
Thrombocytopenia	20 (18)	19 (17)
Petechiae	18 (16)	0 (0)
Chills	17 (15)	1 (1)
Weight decreased	16 (15)	2 (2)
Myalgia	16 (15)	0 (0)
Back pain	15 (14)	0 (0)
Febrile Neutropenia	12 (11)	12 (11)
Pneumonia	12 (11)	10 (9)
Anemia	12 (11)	8 (7)
Weight increased	12 (11)	0 (0)
Bone pain	11 (10)	1 (1)

Myeloid Blast Phase

Reviewer's Table 34. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Dasatinib-Treated Subjects with MB CML

MB CML n=84		
Adverse Event, n (%)	**Any Grade**	**Grade 3/4**
Any	80 (95)	72 (86)
Pyrexia	51 (61)	11 (13)
Diarrhea	43 (51)	8 (10)
Bleeding (any site)	42 (50)	15 (18)
Abdominal pain	29 (35)	3 (4)
Cough	29 (35)	1 (1)
Edema, peripheral	28 (33)	1 (1)
Vomiting	27 (32)	2 (2)
Headache	26 (31)	1 (1)
Nausea	25 (30)	5 (6)
Fatigue	25 (30)	2 (2)
Rash	24 (29)	0 (0)
Dyspnea	24 (29)	7 (8)
Asthenia	21 (25)	7 (8)
Neutropenia	20 (24)	19 (23)
Pleural Effusion	20 (24)	8 (10)
Weight decreased	20 (24)	1 (1)
Anorexia	19 (23)	2 (2)
Thrombocytopenia	17 (20)	17 (20)
Mucositis/stomatitis	14 (17)	3 (4)
Anemia	13 (15)	13 (15)
Bone pain	13 (15)	4 (5)
Pneumonia	12 (14)	7 (8)
Petechiae	12 (14)	1 (1)
Arthralgia	11 (13)	3 (4)
Weight increased	11 (13)	0 (0)
Febrile Neutropenia	10 (12)	10 (12)
Myalgia	9 (11)	2 (2)
Chest pain	9 (11)	2 (2)
Edema, periorbital	8 (10)	0 (0)

Lymphoid Blast and Ph + ALL

Reviewer's Table 35. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Dasatinib-Treated Subjects with LB CML and Ph + ALL

Lymphoid Blast/ Ph + ALL n=81		
Adverse Event, n (%)	**Any Grade**	**Grade 3/4**
Any	80 (99)	67 (83)
Pyrexia	42 (52)	10 (12)
Diarrhea	41 (51)	2 (2)
Nausea	34 (42)	2 (2)
Fatigue	32 (40)	6 (7)
Vomiting	27 (33)	2 (2)
Febrile Neutropenia	22 (27)	20 (25)
Headache	22 (27)	6 (7)
Edema, peripheral	22 (27)	1 (1)
Abdominal pain	22 (27)	5 (6)
Bleeding (any site)	21 (26)	10 (12)
Dyspnea	20 (25)	7 (9)
Rash	20 (25)	3 (4)
Cough	19 (23)	0 (0)
Weight decreased	17 (21)	0 (0)
Asthenia	16 (21)	4 (5)
Pleural Effusion	15 (19)	7 (9)
Weight increased	15 (19)	0 (0)
Bone pain	13 (16)	4 (5)
Myalgia	11 (14)	2 (2)
Chills	11 (14)	0 (0)
Chest pain	10 (12)	2 (2)
Petechiae	10 (12)	0 (0)
Pneumonia	9 (11)	8 (10)
Mucositis/stomatitis	8 (10)	1 (1)
Back pain	8 (10)	3 (4)
Pruritis	8 (10)	0 (0)

Common adverse events in the pooled safety population

Reviewer's Table 36. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Dasatinib-Treated Subjects with CML and Ph + ALL (n=489)

Adverse Event	All Grades (%)	Grade 3/4 (%)
Diarrhea	229 (47)	25 (5)
Pyrexia	192 (39)	33 (7)
Headache	184 (38)	13 (3)
Fatigue	167 (34)	16 (3)
Nausea	152 (31)	9 (2)
Dyspnea	141 (29)	29 (6)
Rash/Exanthem	140 (29)	7 (1)
Peripheral Edema	125 (26)	1 (0.2)
Abdominal pain	122 (25)	11 (2)
Cough	116 (24)	4 (1)
Asthenia	109 (22)	18 (4)
Vomiting	107 (22)	7 (1)
Thrombocytopenia	90 (18)	82 (17)
Pleural Effusion	81 (17)	23 (5)
Anorexia	73 (15)	7 (1)
Weight Decreased	70 (14)	3 (0.6)
Bone pain	66 (13)	10 (2)
Pain in Extremity	61 (12)	2 (0.4)
Constipation	60 (12)	1 (0.2)
Epistaxis	56 (11)	3 (1)
Arthralgia	56 (11)	4 (1)
Anemia	55 (11)	34 (7)
Dizziness	55 (11)	1 (0.2)
Myalgia	54 (11)	4 (0.8)
Neutropenia	52 (11)	50 (10)
Febrile Neutropenia	49 (10)	47 (10)
Petechiae	49 (10)	1 (0.2)
Weight Increased	49 (10)	0 (0)
Chills	47 (10)	1 (0.2)

Summary of common adverse events:

The most common adverse events included gastrointestinal events such as diarrhea (47%), nausea (31%), abdominal pain (25%), and vomiting (22%), constitutional events such as pyrexia (39%), headache (38%), fatigue (34%), asthenia (22%) and anorexia (15%). Fluid retention events such as peripheral edema (26%) and pleural effusion (17%) were also very common. Overall, edema of any type occurred in 40% of all patients and bleeding events of any type in 34%.

The most common grade 3/4 adverse events were hematologic abnormalities. Neutropenia and thrombocytopenia of grade 3 or 4 severity occurred in approximately 45-80% of patients, and

grade 3 or 4 anemia in 18-66%. Investigators were instructed not to report myelosuppressive events as AEs, and so these events are not adequately characterized here.

Chronic phase patients had the fewest common adverse events among the leukemic patients evaluated. Myelosuppression was less common among these patients, as were bleeding events, mucositis, and fever, and febrile neutropenia. Although gastrointestinal complaints were common across all studies, these events were also somewhat less common in patients in CP. As expected, AP patients had an adverse event profile which was more severe than CP but less severe than blast phase patients.

7.1.5.5 Identifying common and drug-related adverse events

Common adverse events were identified using the sponsor's summary adverse event tables and the AESAE datasets. Identification of events as drug-related was complicated by the lack of significant controlled data. However, events that were expected based on class or mechanism of action were considered drug related. Laboratory abnormalities such as neutropenia, anemia, and thrombocytopenia are not included in these tables although commonly reported. These events were felt by the reviewer to be better assessed using the laboratory data tables. The sponsor instructed investigators not to include these events as AEs, so it is likely that any assessment of these events in the AE database would undercount the true incidence of events.

7.1.5.6 Additional analyses and explorations

Not applicable.

7.1.6 Less Common Adverse Events

Adverse events occurring in 2-9% of the safety population are described in Table 37.

Reviewer's Table 37. Less Common Adverse Events in the Safety Population

CML and Ph + ALL (n=489)		
Adverse Event, n (%)	**Any Grade**	**Grade 3/4**
Back pain	46 (9)	5 (1)
Chest pain	45 (9)	6 (1)
Pneumonia	44 (9)	33 (7)
Pruritis	44 (9)	0 (0)
Mucositis/stomatitis	35 (7)	5 (1)
Urinary tract infection	35 (7)	7 (1)
Periorbital edema	35 (7)	0 (0)
Tachycardia	31 (6)	0 (0)
Alopecia	31 (6)	0 (0)
Flatulence	29 (6)	0 (0)
Insomnia	28 (6)	0 (0)
Upper respiratory infection	25 (5)	1 (0.2)
Dyspepsia	25 (5)	0 (0)
Night sweats	24 (5)	0 (0)
Hypertension	23 (5)	2 (0.4)
Dry skin	23 (5)	0 (0)
Hypotension	21 (4)	8 (2)
Paresthesia	20 (4)	1 (0.2)
Depression	20 (4)	0 (0)
Abdominal distension	18 (4)	0 (0)
Dysgeusia/ageusia	18 (4)	0 (0)
Pneumonitis	15 (3)	5 (1)
Sinusitis	14 (3)	4 (1)
Renal failure	12 (2)	12 (2)
Atrial Fibrillation	12 (2)	7 (1)
Palpitations	12 (2)	0 (0)
Hypoxia	11 (2)	7 (1)
Cellulitis	9 (2)	3
Pulmonary hypertension	8 (2)	2

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine laboratory testing including complete blood counts (CBC) and serum chemistries were collected weekly up to week 12 and then every 3 months thereafter for patients with CP CML. CBC, serum chemistries, and coagulation studies (PT/PTT/INR) were collected weekly for patients with AP, MB and LB CML and Ph + ALL.

Creatine kinase (CK) and coagulation studies were collected weekly for the first month, then monthly for 2 months, and then every 3 months thereafter for patients with CP CML. For patients with AP, MB, and LB CML and Ph + ALL, CK and troponin were collected weekly for the first month only.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The safety analysis of dasatinib relies primarily on single-arm data; the one submitted randomized trial is too small (n=36) to provide adequate comparative data. Data from the randomized phase 2 patients who initially received dasatinib are pooled with the data from other studies in CP CML.

7.1.7.3 Standard analyses and explorations of laboratory data

Hematologic Laboratory Abnormalities by Disease Status

Many subjects with advanced disease had baseline hematologic laboratory abnormalities. Across all disease phases, the percent of patients experiencing grade 3/4 neutropenia, thrombocytopenia, and anemia worsened with treatment. Grade 3/4 hematologic abnormalities at baseline and on treatment are summarized below for patients enrolled on the single-arm phase 2 studies in chronic phase, accelerated phase, myeloid blast phase and lymphoid blast/Ph+ ALL.

Reviewer's Table 38. Grade 3/4 Hematologic Laboratory Abnormalities in Patients Receiving Dasatinib

Disease Phase	Neutropenia (% of Patients with)	Thrombocytopenia (% of Patients with)	Anemia (% of Patients with)
Chronic			
--At Baseline	2%	2%	2%
--On Treatment	45%	46%	18%
Accelerated			
--At Baseline	7%	23%	5%
--On Treatment	76%	79%	66%
Myeloid Blast			
--At Baseline	24%	45%	15%
--On Treatment	79%	82%	66%
Lymphoid Blast/Ph+ ALL			
--At Baseline	33%	58%	3%
--On Treatment	76%	78%	49%

Non-hematologic laboratory values

Hypocalcemia

The most common non-hematologic laboratory abnormality arising from dasatinib therapy was hypocalcemia. While pre-treatment hypocalcemia of any grade was found in 8-30% of patients, the incidence of hypocalcemia while on dasatinib was 46-80%. The incidence of grade 3 and 4 hypocalcemia also increased substantially with treatment.

Reviewer's Table 39. Hypocalcemia

Disease Phase	All Grade (% of Patients with)	Grade 3/4 (% of Patients with)
Chronic		
--At Baseline	8%	0.5%
--On Treatment	46%	4%
Accelerated		
--At Baseline	16%	0%
--On Treatment	73%	8%
Myeloid Blast		
--At Baseline	30%	1%
--On Treatment	80%	22%
Lymphoid Blast/Ph+ ALL		
--At Baseline	15%	1%
--On Treatment	67%	13%

None of the patients with normal baseline calcium who experienced a grade 3 or 4 laboratory abnormality on study required any change in dosing due to the event. There were also no reported episodes of muscle spasm, muscle tightness or muscle tension attributable to hypocalcemia. One patient (CA 180015-44-15004) experienced a seizure (grade 3) during a period of grade 3 hypocalcemia. The seizure was attributed to leukemic involvement in the CNS as documented by spinal fluid analysis.

The mechanism of hypocalcemia is unclear. However, in non-clinical studies, dasatinib inhibited parathyroid hormone-stimulated release of calcium dose-dependently and blocked bone resorption.

Hypophosphatemia

Hypophosphatemia was also common on the leukemia studies. This review focuses on grade 3/4 abnormalities. Baseline grade 3/4 abnormalities were uncommon. Treatment-emergent grade 3 hypophosphatemia occurred in 10% of CP patients, 8% of AP patients, 21% of MB patients and 21% of LB Ph+ ALL patients. There were no grade 4 events.

Hyponatremia

Baseline grade 3/4 hyponatremia was uncommon. Treatment-emergent grade 3/4 abnormalities occurred in 2% of CP patients, 10% of AP patients, 13% of MB patients and 17% of LB and Ph+ ALL patients.

Transaminases

Most patients in all phases of disease had normal AST and ALT at baseline. Among those, approximately 50% developed an abnormality in AST, ALT or both while on study. In most cases, these elevations were grade 1/2 in severity; grade 3/4 elevations occurred in 1-9% of patients (1-2% in CP and AP, 4-9% in MB and LB/Ph + ALL.) Changes in AST and ALT were typically transient, resolving over several weeks. Two patients required dose interruptions and reductions for grade 3 or 4 abnormalities. No patient developed symptoms of liver failure.

Bilirubin
Grade 3/4 elevations in bilirubin were uncommon in patients with CP and AP (0% and 2%, respectively) and more common in those with MB (8%) and LB/Ph + ALL (4%). Most patients who developed grade 3 and 4 abnormalities had no recognized precipitating factors; one patient had a history of Gilbert's disease. A dose interruption occurred in one patient due to hepatotoxicity including the abnormal bilirubin, AST and ALT.

Creatinine

Grade 3/4 elevations in creatinine occurred in 9 patients in the safety population. Many of these patients had a prior history of renal disease or chronic illnesses which place them at risk for renal insufficiency, such as diabetes or hypertension. Additionally, concurrent illnesses such as severe infections were likely to have been contributing factors in the development of renal insufficiency in some patients. Two patients required hemodialysis for a grade 3 abnormality. One patient with AP disease developed a grade 3 abnormality while receiving multiple drugs with potential renal toxicity including amphotericin B. Following documentation of the creatinine elevation, dasatinib was interrupted due to endotracheal intubation and the creatinine subsequently improved to grade 1/2. The other patient had LB disease and a history of renal insufficiency but normal baseline creatinine. She developed an elevation in creatinine on study day 15. She received intermittent dialysis, and creatinine had decreased to grade 1 by the time of data cutoff.

Conclusions:

Most laboratory abnormalities that occurred with dasatinib use were more common among patients with advanced stages of disease. Grade 3/4 hematologic laboratory abnormalities were very common among patients receiving dasatinib and increased significantly from baseline in all populations studied. Neutropenia and thrombocytopenia were similar in incidence and more common than anemia.

Among non-hematologic laboratory abnormalities, hypocalcemia was most common overall; hypophosphatemia was also common. Hyponatremia, liver function abnormalities and creatinine

elevations were also noted on study. Most of these abnormailites were reversible or and/or correctable with supplementation. Severe elevations in creatinine occurred primarily in patients with underlying renal disease or concurrent illnesses such as severe infection which placed them at risk for renal insufficiency.

7.1.7.4 Additional analyses and explorations

Not applicable.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

All subjects on the phase 1 and phase 2 studies had weight, blood pressure and heart rate evaluated weekly for the first cycle and at least once per cycle for the remainder of the first 12 weeks while on-study.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The safety analysis of dasatinib relies primarily on single-arm data; the one submitted randomized trial is too small (n=36) to provide adequate comparative data.
The analysis of vitals signs below was performed using the four single-arm phase 2 studies.

7.1.8.3 Standard analyses and explorations of vital signs data

The sponsor reported no significant changes in vital signs for any of the study populations. The reviewer evaluated changes in median blood pressure in patients on the 4 single-arm phase 2 studies.

Reviewer's Table 40. Median Changes in Blood Pressure by Cycle in Study CA180013 (CP CML)

Cycle	Systolic, median (range)	Diastolic, median (range)
Baseline N=185	130 (90-176)	77 (44-100)
1 N=186	128 (78-186)	70 (40-104)
2 N=179	127 (72-185)	72 (10*-99)
3 N=172	125 (92-186)	71 (49-110)
4 N=153	125 (87-160)	71 (46-100)

*probably a transcription error—sys BP was 140

Reviewer's Table 41. Median Changes in Blood Pressure by Cycle in Study CA180005 (AP CML)

Cycle	Systolic, median (range)	Diastolic, median (range)
Baseline N=107	124 (90-105)	75 (50-100)
1 N=107	120 (70-175)	70 (45-100)
2 N=104	120 (80-172)	70 (40-100)
3 N=98	120 (80-169)	70 (40-100)
4 N=89	120 (80-170)	70 (44-105)

Reviewer's Table 42. Median Changes in Blood Pressure by Cycle in Study CA180006 (MB CML)

Cycle	Systolic, median (range)	Diastolic, median (range)
Baseline N=74	124 (93-180)	70 (50-90)
1 N=74	121 (70-165)	70 (40-95)
2 N=61	122 (84-190)	70 (41-93)
3 N=58	120 (79-180)	70 (35-100)
4 N=44	127 (78-178)	70 (45-110)

Reviewer's Table 43. Median Changes in Blood Pressure by Cycle in Study CA180015 (LB/ Ph + ALL)

Cycle	Systolic, median (range)	Diastolic, median (range)
Baseline N=78	122 (90-171)	76 (54-109)
1 N=78	120 (60-187)	70 (40-112)
2 N=61	123 (70-170)	71 (40-104)
3 N=50	120 (90-200)	75 (49-110)
4 N=36	125 (98-160)	77 (50-122)

As demonstrated in the four tables above, there were no clinically significant changes in blood pressure as a result of initiation of dasatinib therapy in any of the leukemic populations.

7.1.8.4 Additional analyses and explorations

Not applicable.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

In preclinical studies, dasatinib was found to have the potential to cause QT prolongation based on the following results:

- Dasatinib inhibited hERG currents dose-dependently. Inhibitions were 6%, 36% and 77% at 3, 10 and 30 μM, respectively. The IC_{50} was calculated to be 14.3 μM.
- Dasatinib prolonged action potential duration (APD) times to 50% and 90% repolarization, in the rabbit Purkinje fiber assay. APD_{50} and APD_{90} were prolonged by 26% and 11%, respectively, following 30 μM BMS354825.

QT prolongation was not observed in the EKG evaluations in the toxicology studies conducted in monkeys.

ECGs were performed prior to treatment, on day 1 and day 8 of the first cycle and at end of treatment in all populations studied. In AP, MB, and LB CML and Ph + ALL, ECGs were also performed after the first and second cycles. In CP CML, after day 8 ECGs were performed every 3 months. ECGs were read by a central laboratory.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The safety analysis of dasatinib relies primarily on single-arm data; the one submitted randomized trial is too small (n=36) to provide adequate comparative data. This analysis therefore focuses on the single-arm trials.

7.1.9.3 Standard analyses and explorations of ECG data

QTc prolongation described as an adverse event was described in section 7.1.3.3

Seven patients who did not have QT prolongation reported as an AE experienced treatment-emergent QTc prolongation of ≥500 msec (QTcB and/or QTcF) as assessed by the central laboratory reading. These findings are described in Table 44.

Reviewer's Table 44. Listing of Patients with On-Study QTc ≥ 500 msec

Patient ID	Longest On-treatment QTcB/QTcF Intervals (msec)	Note
CA180002-1-106	504/469	LBBB present at time of QTc abnormality (QRS=131 msec)
CA180002-1-519	500/475	Multiple QTc intervals > 480 msec pre-dose
CA180005-20-5028	547/510	Pre-dose QTc ≤ 448 msec
CA180005-88-5059	520/461	Pre-dose QTc ≤ 468 msec
CA180006-7-6024	511/489	Pre-dose QTc ≤ 483 msec
CA180006-15-6059	522/491	Pre-dose QTc ≤ 446 msec
CA180006-69-6027	526/478	Pre-dose QTc ≤ 458 msec

Three additional patients with QTc over 500 msec had baseline QTc equal to or higher than the on-study QTc.
Three additional patients with QTc prolongation on central laboratory reading also had QTc prolongation reported as adverse events and were described in section 7.1.3.3. The narratives are summarized below.

One ADR of QTc prolongation (CTC Grade 3, CA180015-56-15066) resulted in dose interruption after 29 days of dasatinib treatment. The QT/QTcB/QTcF intervals for this 35-year-old female subject at the time of the event were 472/568/534 msec, respectively. The event was reported as lasting 6 days although the QTc intervals 2 days later were all <410 msec. The subject also had an isolated ECG abnormality of "abnormal U waves" which was associated with normal QTc intervals. The ADR of QTc prolongation was considered by the Investigator to be probably related to study medication.

The second case (CTC Grade 3, CA180013-1-13018) occurred in a 78-year-old male after 8 days of treatment with dasatinib and resulted in dose interruption. The QT/QTcB/QTcF intervals at the time of the event were 472/499/490 msec, respectively, and were accompanied by an ECG abnormality of RBBB with a QRS interval of 138 msec. The event resolved after 1 day and was considered as possibly related to study medication by the Investigator. Seven days later the subject had an ECG abnormality of prolonged QTc (intervals of 430/503/477 msec) that were again present in the setting of a RBBB. These abnormalities were not considered AEs. This was the last on-study ECG reported in the database.

Finally, patient CA180015-56-15066 experienced a grade 3 QTc prolongation which resulted in dose interruption after 29 days of dasatinib treatment. The QT/QTcB/QTcF intervals for this 35-year-old female subject at the time of the event were 472/568/534 msec, respectively. The event was reported as lasting 6 days although the QTc intervals 2 days later were all <410 msec. The subject also had an isolated ECG abnormality of "abnormal U waves" which was associated with normal QTc intervals.

Mean increase in QTc interval
467 subjects in the 5 phase 2 studies were pooled for the analysis performed by the sponsor. The conclusion was that chronic treatment with dasatinib 70 mg BID was associated with a 3-6

millisecond average increase from baseline in QTcF interval and the upper 95% confidence interval excludes an 8 msec difference.

Overall conclusions of QTc analysis:

- In a pooled analysis of 5 Phase 2 studies in 467 subjects with leukemia, chronic treatment with dasatinib 70 mg BID was associated with a 3-6 millisecond average increase from baseline in QTcF interval.

- Chronic dasatinib treatment in the Phase 2 studies at a dose of 70 mg BID was infrequently associated with QTcF values >500 msec (3 subjects; 0.7%) or QTcF increases from baseline >60 msec (2.9% of subjects).

- There was no relationship between QTc increases and total cumulative exposure.

- Prolonged QTc interval was reported as an SAE in 3 subjects (<1%).

- 2 subjects had 5-beat runs of asymptomatic, non-sustained ventricular tachycardia on Holter ECG recordings. No cases of torsade de pointes were reported.

7.1.9.4 Additional analyses and explorations

Not applicable.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Carcinogenicity studies were not conducted and are not necessary to support the safety of the drug for the proposed leukemia indications.

7.1.12 Special Safety Studies

No special safety studies were submitted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The potential for drug abuse was not investigated or reported in human clinical trials of dasatinib. Symptoms of withdrawal/rebound were not collected, investigated, or reported in human clinical trials of dasatinib.

7.1.14 Human Reproduction and Pregnancy Data

Dasatinib may cause fetal harm when administered to a pregnant woman. In nonclinical studies, at concentrations which are readily achievable in humans receiving therapeutic doses of dasatinib, serious fetal toxicity was observed in both pregnant rats and rabbits.
Fetal lethality was observed in rats.
Dasatinib is therefore not recommended for use in women who are pregnant or contemplating pregnancy. If dasatinib is used during pregnancy, or if the patient becomes pregnant while taking dasatinib, the patient should be apprised of the potential hazard to the fetus.
The potential effects of dasatinib on sperm have not been studied. Sexually active male or female patients taking dasatinib should use adequate contraception. It is not known whether dasatinib is excreted in human milk; therefore women who are taking dasatinib should not breast-feed.

7.1.15 Assessment of Effect on Growth

No clinical studies of sunitinib were carried out in a pediatric population.

7.1.16 Overdose Experience

The highest dose level evaluated in the CML and Ph+ ALL clinical program has been 120 mg BID. The highest dose level evaluated in the Phase 1 Solid Tumor study (CA180003) was 320 mg/day (5 days on, 2 days off schedule), which resulted in DLTs (dose-limiting toxicities) - the next highest dose evaluated in this study was 120 mg BID in the dose schedule.
In the clinical development program, there was 1 overdose reported in a subject with accelerated phase CML in the Phase 1 study (CA180002-1-503). The subject, who was on a 70 mg BID dosing schedule, accidentally took a 200 mg dose of dasatinib instead of 70 mg. Drug was interrupted for 48 hours and the subject was closely monitored. No AEs or change in laboratory parameters related to this overdose were reported.
In the event of overdose, treatment should consist of observation and general supportive measures.

7.1.17 Postmarketing Experience

Not applicable; the drug is not marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The primary data sources for evaluating safety were the six submitted trials performed in subjects with all phases of CML and with Ph + ALL. Five of these trials were single arm studies; the only randomized trial was very small (n=36) and the length of follow-up was very short. This study is therefore inadequate to provide useful comparative data. The safety database therefore consists of approximately 500 patients who had received dasatinib at the phase 2 dose and schedule.

7.2.1.2 Demographics

The age and gender distributions of patients were appropriate to the disease under study. Almost all patients across the clinical program were white. Conclusions about the safety of dasatinib in races other than white can not be drawn from this database.

Extent of exposure (dose/duration)

489 patients with all phases of CML and with Ph + ALL were studied across the clinical program and are included in the safety analysis. Most patients on the studies had received between 3-6 months of dasatinib at the time of NDA submission; about a third had received less than 3 months and approximately 10% had received greater than 6 months of dasatinib.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable.

7.2.2.1 Other studies

No studies other than those described above were used in the safety analysis.

7.2.2.2 Postmarketing experience

The drug is not marketed inside or outside the U.S.

7.2.2.3 Literature

There are no literature reports relevant to the safety evaluation of dasatinib.

7.2.3 Adequacy of Overall Clinical Experience

The safety database for this application contains an adequate number of subjects, with nearly 500 patients with all phases of CML and Ph + ALL. Major limitations include the limited duration of exposure and the lack of randomized study data.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Special animal and *in vitro* testing was adequate.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Overall, the metabolic, clearance and interaction workup was adequate. Two outstanding clinical pharmacology studies will be the subject of a phase 4 commitment: submission of the ongoing ketoconazole study and submission of the ongoing hepatic impairment study. Additionally, the clinical pharmacology team recommended that an *in vivo* study to evaluate dasatinib as an inhibitor of P-glycoprotein be performed.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Based on the preclinical findings and known adverse events of drugs in this class, the evaluation for potential adverse events was adequate. Based on the high number of dose reductions and interruptions required due to toxicity, as well as evidence of drug activity at a lower dose (50 mg bid), dasatinib should be thoroughly evaluated for safety and efficacy at 50 mg bid.

7.2.8 Assessment of Quality and Completeness of Data

Data were complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

The safety update (SU) was submitted on April 27, 2006. Data tables were not submitted for this safety update. The sponsor's table below describes the breakdown of patients included in this update.

Table 45. Safety Update---Breakdown of Dasatinib-Treated Subjects

Table 2.1A: Dasatinib-treated Subjects; 120-Day SU Cohort

	Number of Subjects				
Study	Chronic CML	Accelerated CML	Myeloid Blast CML	Lymphoid Blast CML/Ph+ ALL	Total
CA180002	NA[a]	12	23	11	46
CA180005	0	174	0	0	174
CA180006	0	0	109	0	109
CA180013	387	0	0	0	387
CA180015	0	0	0	94	94
CA180017	101	0	0	0	101
Total	488	186	132	105	911

NA - Not applicable

[a] 23 chronic CML subjects with BID dosing and 22 subjects with QD dosing were treated. These data remain unpooled because of the different dosing regimens used with respect to the safety cohort

The sponsor included data from all the studies included in the NDA submission. There were no additional studies included.

Duration of exposure

As shown in Table 46, the majority of subjects in the 120-Day SU cohort (57%; N = 517) had a duration of > 6 months of treatment. Twenty-three percent (N = 207) were treated for 3 to 6 months, and 21% (N = 187) were treated for 3 months or less.
Among the 400 subjects in the 120-Day SU cohort not included in the NDA, the duration of treatment was < 3 months in 62 (16%) subjects, between 3 to 6 months in 146 (36%) subjects, and > 6 months in 192 (48%) subjects.

Table 46. Total Duration of Dasatinib Exposure—Sponsor's SU Table 4.1

	Number (%) of Subjects		
Duration	NDA Cohort	NDA SU Cohort	120-Day SU Cohort
N	511	511	911
Median (months)	4	8	6
Min - Max	0 - 13	0 - 19	0 - 19
≤ 3 months	166 (32)	125 (24)	187 (21)
3 - ≤ 6 months	289 (57)	61 (12)	207 (23)
> 6 months	56 (11)	325 (64)	517 (57)

Deaths

A total of 102 deaths were reported within 30 days of dasatinib dosing across the 911 patient SU population (11%). An additional 3 deaths were not within 30 days of dosing, but were attributed to study drug toxicity. These three deaths were reportedly due to BM failure, global cardiac insufficiency, and pleural effusion. The patient reported as global cardiac insufficiency was reported in the original NDA submission; this was the first report for the two others.

Of the 102 subject deaths within 30 days of dosing, 52 were attributed to disease progression, 23 to infection, and 8 to bleeding, including 6 intracranial hemorrhages. Fifteen deaths were attributed to other causes including fluid retention (one each of cardiac failure, pleural effusion, pericardial effusion and pulmonary edema), massive MI (1 patient) and pulmonary embolism (1 patient). The cause of death in 4 patients was listed as unknown.

Two patients died of intracranial hemorrhage since the original NDA submission, bringing the total number of fatal CNS bleeding events to 7 (Note: there is one death reported in the review that was not reported by the sponsor, which occurred on the phase 1 dose escalation study. This patient received a dose of dasatinib other than 70 mg bid). Both of these patients were on study 180015 (lymphoid blast/Ph + ALL). In one patient, the platelet count had fluctuated from a baseline of 17,000, up to 31,000. The last recorded platelet count was 27,000 on August 18, 2005. Death occurred on . The other, whose cause of death was listed as "probable" intracranial hemorrhage, had a baseline platelet count of 17, which had improved to over 100,000 by study day 71. The last platelet count available in the NDA submission was July 14th, at which time it was 107,000. The patient died

One patient included in the original safety cohort but updated in the safety update was reported to have died due to cardiac failure. This patient was a 72 year old male who discontinued study drug on May 17, 2005 due to disease progression. , he died of "acute heart failure". There is no evidence of CHF or fluid retention events in the AEs listed prior to his death and there is no other information available regarding his death.

Drug-Related Edema

The safety update contains a summary of drug-related edema events. There is no description of all-causality events. Overall approximately 25% of patients experienced one or more edema events which were deemed drug-related. Most events were considered to be "superficial" rather than generalized edema. The incidence of edema in the original submission is 15% higher, however, this is "all-causality" edema rather than "drug-related" edema. Peripheral edema accounted for the majority of cases of edema in both submissions. The category "face edema" below corresponds well with the incidence of facial and periorbital edema in the original submission.

Table 47. Drug-Related Superficial and Generalized Edema—Sponsor's Table 5.6.1 A (120 Day Safety Update)

Number (%) of Subjects

Drug-related Terms	Chronic N = 488	Accelerated N = 186	Myeloid Blast N = 132	Lymphoid Blast N = 105
ALL EDEMA	111 (23)	52 (28)	41 (31)	22 (21)
GRADE 3 TO 4	1 (<1)	2 (1)	2 (2)	1 (1)
INTERRUPTION FOR ANY EVENT	4 (1)	5 (3)	2 (2)	2 (2)
DISCONTINUATION	0	1 (1)	0	0
SUPERFICIAL EDEMA	106 (22)	52 (28)	38 (29)	22 (21)
FACE EDEMA[a]	53 (11)	22 (12)	17 (13)	12 (11)
OTHER SUPERFICIAL EDEMA[b]	0	2 (1)	0	0
PERIPHERAL EDEMA[c]	69 (14)	41 (22)	28 (21)	16 (15)
GENERALIZED EDEMA[d]	11 (2)	7 (4)	9 (7)	3 (3)
GRADE 3 TO 4	1 (<1)	0	1 (1)	1 (1)

[a] Includes eye edema, eye swelling, eyelid edema, orbital edema, face edema, periorbital edema, and swelling face

[b] Includes genital edema and scrotal edema

[c] Includes gravitational edema, localized edema, and edema peripheral

[d] Includes edema, generalized edema, fluid retention, and fluid overload

Other fluid retention events

The following fluid retention events were reported in patients included in the 120 day safety cohort. All-grade events were summarized regardless of causality assessment.
Grade 3/4 events were summarized by the sponsor only if they were assessed as drug related.

Reviewer's Table 48. Fluid Retention Events Including Cardiac Failure in the Safety Update Population

	Chronic N=488	Accelerated N=186	MB N=132	LB/Ph+ ALL N=105	Total N=911
Congestive Heart Failure	16 (3)	3 (2)	5 (4)	1 (1)	25 (3)
Drug-Related Grade 3/4	9 (2)	0 (0)	2 (2)	0 (0)	11 (1)
Cardiac Dysfunction	4 (1)	3 (2)	4 (3)	0 (0)	11 (1)
Drug-Related Grade 3/4	3 (1)	1 (1)	3 (2)	0 (0)	7 (1)
Pulmonary Edema	10 (2)	9 (5)	7 (5)	6 (6)	32 (4)
Drug-Related Grade 3/4	3 (1)	2 (1)	0 (0)	0 (0)	5 (1)
Pulmonary Hypertension	5 (1)	1 (1)	4 (3)	0 (0)	10 (1)
Drug-Related Grade 3/4	1 (<1)	0 (0)	1 (1)	0 (0)	2 (<1)
Pericardial Effusion	8 (2)	7 (4)	15 (11)	4 (4)	34 (4)
Drug-Related Grade 3/4	1 (<1)	1 (1)	3 (2)	0 (0)	5 (1)

Gastrointestinal Bleeding Events
The sponsor reported an overall incidence of all-causality GI hemorrhage of 14%. These bleeding events were more common in patients with AP (25%), MB (27%) and LB/ Ph + ALL (15%) than in CP (5%). Grade 3/4 events were summarized only if drug related and occurred in 5% of patients.

CNS Bleeding Events
In addition to the deaths reported above, the sponsor reported a total of 7 subjects with drug-related CNS bleeding events. There was no report of the total number of CNS hemorrhages provided in the safety update.

Bleeding events other than GI or CNS
The sponsor reported two-hundred and ninety-nine (33%) subjects in the 120-day cohort had a hemorrhagic or bleeding event excluding GI or CNS hemorrhages. Of those, 17% were considered drug-related.

QT abnormalities
The sponsor reported an additional 3 patients with "drug-related" QT or QTc prolongation compared to the initial submission (one corrected and two uncorrected).

Safety Update Conclusions: The safety update included 911 patients, an increase of approximately 400 patients compared to the original NDA submission. The median duration of follow-up was also longer in the SU population. No new safety signals emerged from review of the SU data.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Adverse events which were most likely to be disease related included fluid retention events including pleural effusions and peripheral edema, myelosuppression (neutropenia, thrombocytopenia, and anemia), hypocalcemia and hypophosphatemia. Other events which may be related to dasatinib use include gastrointestinal events such as diarrhea, nausea, abdominal pain and vomiting, QT prolongation and bleeding events.
The ability to assess causality of adverse events in this application is limited by the lack of sufficient randomized data. One randomized study was included in the submission, however, the number of patients treated was very small (n=36) and the duration of treatment was too short to adequately assess for differences in toxicity between the two treatment arms.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Common adverse events were evaluated both by disease population and for the pooled leukemia population. In the case of the analyses by disease population, these analyses did include data from 2-3 studies (phase 2 + phase 1 data) but included only those patients receiving the 70 mg bid dose.
Adverse event data across the phases of disease were combined in one analysis of the common adverse events and in the analysis of less common events and events considered to be significant (e.g. bleeding events, fluid retention events, QT prolongation and cardiac failure). Where relevant, differences in incidence between different disease populations were described (for example, febrile neutropenia).

7.4.1.2 Combining data

Data were pooled by combining the numerator events and the denominators for the studies. No weighted pooling was performed.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Only the 70 mg bid dose was thoroughly evaluated with respect to adverse events as there were insufficient numbers of patients treated at other doses to perform an adequate safety evaluation.

7.4.2.2 Explorations for time dependency for adverse findings

Time to event for certain significant adverse events (e.g. cardiac failure events) was reported under the review of the relevant events in section 7.1. Evaluations for adverse events occurring with long term administration (> 6 months) could not be performed due to the limited duration of exposure in the submitted studies.

7.4.2.3 Explorations for drug-demographic interactions

There were no apparent differences in the safety profile of dasatinib based on patient age (< 65 vs. ≥ 65 years of age) or gender. There were too few non-white patients to perform a comparative evaluation of safety.

7.4.2.4 Explorations for drug-disease interactions

All patients evaluated had CML or Ph + ALL. Most adverse events were more common in patients with more advanced disease and in most cases these events are expected based on the natural history of the disease. No further evaluation of drug-disease interaction was examined.

7.4.2.5 Explorations for drug-drug interactions

No formal analyses of drug-drug interactions were performed as part of the clinical review. Patients on the leukemia studies were often receiving multiple concomitant medications. No drug interactions were apparent.
See the clinical pharmacology review for information regarding interactions with medications which affect the gastric pH and drugs which induce, inhibit or are metabolized by the cytochrome P450 enzyme 3A4.

7.4.3 Causality Determination

Nearly all the adverse event data was obtained from single-arm trials, complicating the issue of determining causality. The gastrointestinal toxicities and fluid retention events are likely drug related events. Myelosuppression and hypocalcemia also appear to be caused by dasatinib. Given the nature of the disease, it is difficult to ascertain whether drug or disease is responsible for the high incidence of bleeding events, infections and neutropenic fevers. However, since these events are associated with myelosuppression, it is likely that some of these events are caused by dasatinib.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The Sponsor's recommended dasatinib starting dose for patients with all phases of CML and with Ph+ ALL is 70 mg BID. This dose was used in all Phase 2 studies. Responses were also

seen at lower doses in a limited number of patients. There is currently not enough data to recommend a starting dose other than 70 mg BID. However, since many patients receiving 70 mg BID required dose interruptions and reductions due to toxicity, the reviewers recommend that the sponsor study the safety and efficacy of dasatinib at a lower dose (e.g. 50 mg BID).

8.2 Drug-Drug Interactions

Dasatinib is metabolized mainly by CYP3A4. Drugs that inhibit CYP3A4 activity decrease the rate of dasatinib metabolism and increase dasatinib plasma concentrations. Dasatinib is an inhibitor of CYP3A4 and may decrease the metabolic clearance of drugs that are primarily metabolized by CYP3A4. CYP3A4 inducers, such as rifampicin, decrease dasatinib plasma concentrations. Dasatinib increases plasma concentrations of CYP3A4 substrates, such as simvastatin.

Antacids and proton pump inhibitors, such as famotidine, reduce plasma concentrations of dasatinib.

8.3 Special Populations

- No age- or gender-related differences in efficacy or safety of dasatinib were apparent.
- No conclusions can be made on any race-related differences in efficacy or safety of dasatinib, because fewer than 10% of patients in clinical studies were non-White.
- Dasatinib has not been studied in patients with hepatic or renal impairment.

8.4 Pediatrics

Dasatinib has not been studied in pediatric populations.

8.5 Advisory Committee Meeting

This application was presented at Oncologic Drugs Advisory Committee meeting on June 2, 2006 at Omni Hotel in Atlanta, GA. The questions to the Committee and the votes by the Committee are shown below.

Food & Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Oncologic Drugs Advisory Committee Meeting
June 2, 2006
Omni Hotel, Atlanta GA

Dasatinib (Sprycel) Bristol-Myers Squibb Company

Meeting Questions:

1. The Agency has accepted durable responses in hematologic malignancies for approval for both chronic leukemias (accelerated approval) and acute leukemias (regular approval). The FDA granted Gleevec® (imatinib) accelerated approval for chronic, accelerated, and blast crisis phases of CML based on durable major cytogenetic responses and major hematologic responses.

   Based on the magnitude and duration of responses (Table 1 and 2), has the sponsor provided sufficient evidence of dasatinib's effectiveness for the following: Chronic phase CML? Accelerated phase CML? Myeloid blast CML? Lymphoid blast CML?

Table 1. FDA: Cytogenetic and Hematologic Responses – Percentages of All Phase 2 Subjects

Disease phase (N=number of subjects)	MCyR (%)	MaHR (%)
Chronic phase, N = 186	45	--
Accelerated phase, N = 107	31	59
Myeloid blast phase, N = 74	30	32
Lymphoid blast phase, N=42	50	31
Philadelphia-positive (Ph +) acute lymphoblastic leukemia (ALL) N=36	58	42

Table 2. FDA Response Duration

	Chronic phase	Accelerated phase	Myeloid blast	Lymphoid blast	Ph + ALL
Duration of response (months), median (95% CI)	Not reached*	Not reached*	Not reached*	3.7 (2.8 – not reached)	4.8 (2.9- not reached)

* Approximately 100% of responders are in response at 6 months.

(If the answers to question #1 are no, please proceed to question 4.)

For approval – imatinib-resistant populations (except Philadelphia-positive ALL). For approval – imatinib-intolerant population (except Philadelphia-positive ALL)

Committee Vote: Yes (unanimous, 14/14).

2. The major toxicities observed with dasatinib include the following: gastrointestinal and hematological toxicities, fluid retention, bleeding, and myelosuppression. Less frequent, but serious, adverse events include cardiac toxicity and intracranial bleeding. Based on the phase 2 data, does the risk/ benefit profile support dasatinib's approval for the following: Chronic phase CML? Accelerated phase CML? Myeloid blast CML? Lymphoid blast CML?

Committee Vote: **Yes (unanimous, 14/14).**

3. Imatinib intolerance was defined as either 1) imatinib-related toxicity leading to imatinib discontinuation, or 2) inability to tolerate imatinib. The number of intolerant patients enrolled per study (except for the chronic phase CML studies) was less than 10%. Based on the data presented in Table 3, has the sponsor provided evidence of an effect on a surrogate endpoint (major cytogenetic response) for chronic phase CML patients intolerant to Gleevec?

Committee Vote: **Yes, 13/14; Abstained, 1/14.**

Based on the data presented below, has the sponsor provided sufficient evidence to warrant accelerated approval in CML patients intolerant to imatinib in either Accelerated, Myeloid blast, or Lymphoid blast phases?

Committee Vote: **Yes (unanimous, 14/14).**

FDA Table 3. Summary of MCyR and MaHR Responses in Imatinib-Intolerant and Imatinib-Resistant Subjects in All Studies

Disease phase	Intolerant N = 94		Resistant N = 457	
	MCyR	MaHR	MCyR	MaHR
Chronic	49/67 (73%)		62/181 (34%)	
Accelerated		7/12 (58%)		62/106 (58%)
Myeloid blast		1/7 (14%)		30/90 (33%)
Lymphoid blast		2/6 (33%)		14/41 (34%)
Ph+ ALL		2/2 (100%)		14/39 (36%)

For approval – Philadelphia-positive ALL

4. As stated above, the FDA has approved drugs to treat acute leukemias based on durable complete responses. The sponsor has presented data (major hematological responses) for Philadelphia-positive acute lymphoblastic leukemia patients who have experienced disease progression on imatinib and other therapies. Based on the data presented in the above tables, has dasatinib demonstrated sufficient evidence to warrant regular approval in either the imatinib-resistant or intolerant Philadelphia-positive ALL populations?

Committee Vote: **Yes, 12/14; No, 1/14; Abstained, 1/14.**

5. Accelerated approval requires a commitment to perform a confirmatory clinical trial to demonstrate clinical benefit. Please discuss future study designs to accomplish this goal. These trials could be either front-line or relapsed disease settings.

Committee Suggestions: 1) Continuation of ongoing trials, 2) Trials to determine recommended dose, 3) Molecular markers, and 4) Determination whether treatment needs to be continued for life, and whether dose can be decreased subsequent to response.

8.6 Literature Review

References are cited in the text of the review. A comprehensive literature review was not performed.

8.7 Postmarketing Risk Management Plan

A postmarketing risk management plan has not been submitted.

8.8 Other Relevant Materials

On May 4, 2006, DDMAC objected to the proposed name, "Sprycel".

Sprycel

DDMAC objects to the proposed trade name Sprycel

The division felt that the name Sprycel has an advantage in that it will not be easily mistaken for another drug.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy:

- Dasatinib is an inhibitor of multiple protein tyrosine kinases (such as the SRC family of kinases [including SRC, LCK, YES, and FYN], c-KIT, EPHA2, and PDGF-Rβ), including BCR-ABL. As shown in four single-arm studies, treatment with dasatinib resulted in hematologic and cytogenetic responses in patients with all phases of CML and with Ph+ ALL who are imatinib-resistant or who are intolerant of imatinib. The patients had long histories of disease and had undergone extensive treatment with various modalities.
- The four major Phase 2 trials were uncontrolled single-arm studies, because there is no effective comparator drug and a placebo control is deemed to be unethical, as historically patients with advanced stages of CML and with Ph+ ALL are known to not have spontaneous cytogenetic or hematologic responses and generally have short survivals. The small controlled trial showed that 79% of patients randomized to the high dose imatinib arm crossed over to the dasatinib arm. Therefore, effectiveness of dasatinib in imatinib resistant or imatinib intolerant population is based on historical evidence of interferon efficacy.
- The primary endpoints chosen depended upon the disease phase being studied – cytogenetic response (MCyR) in CP CML and hematologic responses (MaHR and OHR) in advanced-phase CML and in Ph^+ ALL – because of concern that marrow fibrosis and poor marrow reserves might preclude cytogenetic analysis in patients with advanced phase disease. Cytogenetic response became a secondary efficacy endpoint in advanced phases of CML.
- MCyR rates were 45% in CP CML, 31% in AP CML, 30% in MB CML, 50% in LB CML, and 58% in Ph+ ALL. In CP CML CHR rate was 90%. MaHR rates were 59% in AP CML, 32% in MB CML, 31% in LB CML, and 42% in Ph+ ALL.
- Most hematologic and cytogenetic responses occurred during the first 3 months of treatment..
- Cytogenetic and hematologic responses were relatively durable. In these ongoing studies nearly all CP, AP and MB CML patients with responses remained in response at the 6-month data cutoff. Median durations of MaHR were 3.7 months in LB CML patients and 4.8 months in Ph+ ALL patients.
- Cytogenetic and hematologic responses were associated with lower rates of disease progression.
- No age- or gender-related response differences were apparent.
- Response rates were higher in imatinib-intolerant than in imatinib-resistant CP CML patients.
- On the basis of the dose determination study, the Sponsor concluded that the starting dose for all Phase 2 studies was 70 mg BID and this dose was used in all single-arm trials. In the Reviewer's opinion, the dose determination study did not define a dose-response

relationship. The optimal dose with respect to efficacy appears to be 50 - 70 mg BID in all populations studied (CP CML, AP CML, MB CML, LB CML and Ph^+ ALL).

- Dasatinib is an effective drug in patients with all phases of CML and with Ph^+ ALL who are resistant to or intolerant of imatinib and who, therefore, have limited treatment options.
- Responses are reasonably likely to predict clinical benefit and therefore support accelerated approval in CML patients. Regular approval may be granted when results of completed trials with 24-month follow-up are submitted.
- Dasatinib may be granted regular approval for treatment of patients with Philadelphia chromosome-positive ALL, because response rates have been considered evidence of clinical benefit in acute leukemia meriting regular approval.

Safety

Four-hundred-and-eighty-nine (489) patients with all stages of CML and Ph + ALL were included in the safety population, including 214 patients with CP CML , 110 with AP, 84 patients with MB CML and 81 patients with LB CML or Ph + ALL. All these patients received a starting dose of dasatinib of 70 mg BID.

Most patients (57%) had 3-6 months of exposure to dasatinib, while 32% were treated for less than 3 months and 11% were treated for more than 6 months.

Dose modifications were common in all populations studied with dose reductions occurring in 21-50% of patients and dose interruption in 68-82% of patients. Dose adjustments were more common in patients with earlier stage disease, largely due to dose modifications for hematologic toxicity. Dasatinib was discontinued due to adverse events in 4-6% of patients with CP CML and AP CML, and in 13-15% of patients with MB CML, LB CML and Ph + ALL.

The most common adverse events included gastrointestinal events such as diarrhea (47%), nausea (31%), abdominal pain (25%), and vomiting (22%), constitutional events such as pyrexia (39%), headache (38%), fatigue (34%), asthenia (22%) and anorexia (15%). Fluid retention events such as peripheral edema (26%) and pleural effusion (17%) were also very common. Overall, edema of any type occurred in 40% of all patients and bleeding events of any type in 34%.

The most common grade 3/4 adverse events were hematologic abnormalities. Neutropenia and thrombocytopenia of grade 3 or 4 severity occurred in approximately 45-80% of patients, and grade 3 or 4 anemia in 18-66%. These abnormalities were least common in CP CML and of similar incidence in all other stages of disease.

Other common grade 3/4 events included neutropenic fever (10%), bleeding events (10%), pyrexia (7%), dyspnea (6%), pleural effusion (5%), and diarrhea (5%).

Other significant adverse events included CNS hemorrhages occurring in 6 patients, 5 of which were fatal. All but one event occurred in patients with advanced disease. Cardiac failure occurred in 4% of patients; most of these patients had cardiac risk factors such as hypertension.

QTc prolongation reported either as an adverse event or on central laboratory reading (> 500 msec) was reported in 3% of patients. The average increase in QTcF from baseline was 3-6 milliseconds.

9.2 Recommendation on Regulatory Action

Accelerated approval should be granted for dasatinib for use in the treatment of adults with chronic phase (CP), accelerated phase (AP), or myeloid or lymphoid blast (MB or LB) phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate.

Regular approval should be granted for dasatinib for use in the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph^+ ALL) with resistance or intolerance to prior therapy.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The sponsor should provide periodic safety reporting and continue post-marketing surveillance activities.

9.3.2 Required Phase 4 Commitments

- Completion of ongoing, single-arm Phase 2 studies in patients with CP CML (CA180013), AP CML(CA180005), and MB CML (CA180006) who are resistant to or intolerant of imatinib mesylate, and in patients with LB CML (CA180015) who are resistant to or are intolerant of prior therapy.
- Submission of the ongoing study of ketoconazole on dasatinib PK.
- Submission of ongoing study of dasatinib PK in hepatic impairment.

9.3.3 Other Phase 4 Requests

- Completion of ongoing, single-arm Phase 2 studies in patients with Ph^+ ALL (CA180015) who are resistant to or are intolerant of prior therapy.
- Completion of the four-arm study (CA180034) examining optimal dose and schedule (100 mg QD vs. 140 mg QD vs. 50 mg BID vs. 70 mg BID) in CP CML.
- An *in vivo* study of dasatinib as inhibitor of P-gp.

9.4 Labeling Review

The submitted product labeling was extensively revised. The labeling is not finalized at the time of filing of this review.

9.5 Comments to Applicant

Will be sent with the action letter.

APPEARS THIS WAY
ON ORIGINAL

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 CA180002. A Phase I Dose-Escalation Study to Determine the Safety, Pharmacokinetics, and Pharmacodynamics of BMS-354825 in the Treatment of Patients with Chronic, Accelerated, or Blast Phase Chronic Myelogenous Leukemia, or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Who Have Hematologic Resistance to Imatinib Mesylate (Gleevec®).

Study Status: The study was started on November 6, 2003 and is ongoing. Accrual was closed on May 11, 2005 with a total of 92 enrolled subjects.
Study Objectives:
Primary Objective: To establish the MTD, maximum administered dose (MAD), DLTs, and a recommended Phase 2 dose of dasatinib in subjects with CML and Ph+ ALL who had hematologic resistance to or intolerance of imatinib.
Secondary Objectives: Safety and tolerability, plasma PK, preliminary evidence of efficacy, effects on biomarkers of BCR-ABL, SRC-related protein expression and SRC kinase activities, and mechanisms of resistance of CML and Ph+ ALL to imatinib by analysis of BCR-ABL point mutations.

Study Design: Eligible subjects were treated with dasatinib orally either QD or BID on one of two schedules (5 days on and 2 days off, or continuous dosing). The doses ranged from 15 mg/day to 240 mg/day. Subjects were enrolled at 2 centers.

> Note: MTD and a recommended Phase 2 dose were to be defined by DLTs occurring in the first 4 weeks of treatment. However, during the conduct of the trial, it became apparent that subjects remained on study for extended periods of time due to continued efficacy. Subjects in the lower dose cohorts were typically escalated after the first 4 weeks of treatment to maximize hematologic and cytogenetic responses.

Study Population: Inclusion criteria for CP, AP, MBP and LBP CML, and Ph+ ALL patients with a primary or acquired hematologic resistance to imatinib or intolerance to imatinib are defined in studies CA180013, CA18005, CA18006, CA180015, and CA180017.

The number of subjects accrued was 92, of whom 91 were treated. Efficacy data is provided on the first 84 subjects, who were enrolled by February 15, 2005 and had a minimum 3 months follow-up.

Treatments Administered: Subjects began dasatinib treatment either on a QD schedule or on one of two BID schedules (5 days on and 2 days off, or continuous dosing). The majority of subjects on the 5 days on/2 days off schedule were escalated to continuous daily dosing. For this reason, subjects in both schedules are grouped together in the analysis of results. Treatment administration plan is shown in Reviewer's Table A1 (Sponsor's Table 3.4.1).

Reviewer's Table A1. CA180002. Dasatinib Administration Schedules

Cohort	Dosing Regimen	Dose Levels (mg/day)
Chronic	QD 5 days on/2 days off	15, 30, 50, 75, 105, 140,180
Chronic	BID 5 days on/2 days off	25, 35, 50, 70
Chronic	BID continuous	70
Accelerated	BID continuous	50, 70, 90, 120
Myeloid Blast	BID continuous	50, 70, 90, 120
Lymphoid Blast/ALL Ph+	BID continuous	35, 50, 70, 90

Dose escalation: The starting dose for each cohort is shown in the Reviewer's Table A1. Three subjects were enrolled per cohort and followed for 4 weeks on study drug. If a DLT was observed, that dose cohort was expanded to 6 subjects. Dose escalation continued as long as there was less than 1 of 3 subjects in a cohort with DLT. Some subjects were added to lower, previously filled dose levels in order to obtain further safety and efficacy information. This accounts for some dose levels with more than 6 subjects.

Intra-subject dose escalation was permitted, if the subject's maximum toxicity was grade ≤ 2, subject had completed 4 weeks at the initially assigned dose level, and all 3 subjects at the next higher dose level completed 4 weeks with no DLT.

Dose modifications are described for the management of toxicity or disease progression. Parameters for dose interruption or reduction and for treatment discontinuation are described for non-hematological adverse events and for hematologic adverse events in chronic phase CML and for advanced phase CML/Ph+ ALL.

DLT was defined as any of the following events attributed to dasatinib and occurred during the first 4 weeks of drug administration: grade 3 or 4 nausea, vomiting or diarrhea; any other grade 3 or greater non-hematological toxicity; delayed recovery from non-hematological toxicity (> 14 days), QTc > 500 msec; grade 4 neutropenia for => 7 consecutive days or thrombocytopenia or bleeding requiring platelet transfusion (chronic phase CML); grade 4 neutropenia for => 21 days or febrile neutropenia and sepsis (accelerated or blast phase CML).

MTD was defined the dose level below MTD, provided DLT was observed in < 1/3 subjects at that dose level.

Concomitant Treatment
Anagrelide for platelet counts > 700,000/mm^3, hydroxyurea for WBC > 50,000/mm^3, CSF and erythropoietin permitted. Medications associated with QT prolongation, with platelet function inhibition, and anticoagulants prohibited. CYP3A4 substrates, inhibitors, and inducers were, if possible, avoided.

Efficacy Assessments: as described above under each study for each population.

Protocol Deviations: Seven of 84 subjects had a significant protocol deviation: 5 had inadequate metaphases to confirm Ph+ status, 2 lacked some criteria for chronic phase CML (combining data from two dates resulted in meeting these criteria).

Disposition of Subjects: At the time of data cutoff, 50/84 (60%) were on treatment, 34/84 (40%) were off treatment. The major reason for discontinuation of treatment was disease progression, in 19/84 (23%) of subjects. Most of the subjects who progressed, 14 of 19, had myeloid blast CML or lymphoid blast/Ph+ ALL. Subject disposition is shown in Reviewer's Table A3 (Sponsor's Table 5.1).

Reviewer's Table A2. CA180002. Subject Disposition – All Treated Subjects

Subject Disposition	Chronic QD N=21	Chronic BID N=19	Accelerated N=11	Myeloid Blast N=23	Lymphoid Blast/Ph+ ALL, N=10	Total N=84
On Treatment	19 (91%)	17 (90%)	7 (64%)	6 (26%)	1 (10%)	50 (60%)
Off Treatment	2 (10%)	2 (11%)	4 (36%)	17 (74%)	9 (90%)	34 (40%)
Dis. Progr.	1	1	3	8	6	19 (23%)
Death	0	0	0	6	1	7 (8%)
Subj. Req.	1	0	0	0	0	1 (1%)
Other	0	1	1	3	2	7 (8%)

Demographic and Other Baseline Characteristics: Demographic characteristics were similar to those presented in studies under each disease category and phase (Reviewer's Table A3; data from Sponsor's Table 5.3).

Reviewer's Table A3. Demographic Characteristics – All Treated Subjects

Characteristic	**Total, N = 84**
Age, years	
Mean ± SD	56 ± 14
Median	56
< 65	55 (65%)
>= 65	29 (35%)
Gender	
Male	47 (56%)
Female	37 (44%)
Race	
White	64 (76%)
Black/African American	10 (12%)
Asian	4 (5%)
Other	6 (7%)

ECOG PS	
0	52 (62%)
1	29 (35%)
2	3 (4%)

Disease History and Baseline Hematologic Status: A summary of the disease history for imatinib-resistant (83%) and imatinib-intolerant (17%) subjects is shown in Reviewer's Table A4 and baseline hematologic status in Table A5. The median time from the initial diagnosis of CML to the first dose of dasatinib ranged from 100 months (range, 36 to 207 months) in chronic phase BID group to 26 months (range, 9 to 70 months) in lymphoid blast/Ph + ALL group. The majority of subjects were heavily pretreated.

Reviewer's Table A4. Disease History – All Treated Subjects

	Chronic QD N=21	**Chronic BID N=19**	**Accelerated N=11**	**Myeloid Blast N=23**	**Lymphoid Blast/Ph+ ALL, N=10**	**Total N=84**
Length of disease (months)	79 (13 – 151)	100 (36 – 207)	67 (22 – 139)	44 (5 – 216)	26 (9 – 70)	
Prior BM Transplant	2 (10%)	0	0	5 (22%)	5 (50%)	12 (14%)
Prior chemotherapy	9 (43%)	13 (68%)	4 (36%)	15 (65%)	9 (90%)	50 (60%)
Prior interferon	18 (86%)	19 (100%)	9 (82%)	12 (52%)	2 (20%)	60 (71%)
Hydroxyurea/ Anagrelide	21 (100%)	19 (100%)	10 (91%)	18 (78%)	5 (50%)	73 (87%)

Reviewer's Table A5. CA180002. Baseline Hematologic Status – All Treated Subjects

	Chronic QD N=21	**Chronic BID N=19**	**Accelerated N=11**	**Myeloid Blast N=23**	**Lymphoid Blast/Ph+ ALL, N=10**
Extramedullary involvement					
spleen	0	0	0	0	0
outside spleen	0	0	0	6 (26%)	1 (10%)
WBC median (range) (/mm³)	20,300 (2,800 – 185,000)	43,000 (2,900 – 242,600)	20,600 (1,300 – 107,700)	20,500 (300 – 117,300)	11,600 (1,200 – 197,600)

Platelets/mm³ Median (range)	327,000 (87,000 – 2,166,000)	300,000 (52,000 – 897,000)	279,000 (4,000 – 1,710,000)	39,000 (7,000 – 1,057,000)	40,500 (22,000 – 375,000)
PB basophilia Median % (range)	5% (0% - 25%)	4% (0% - 19%)	14% (0% - 44%)	2% (0% - 26%)	0.5% (0% - 3%)
Blasts in PB Median % (range)	0% (0% - 14%)	0% (0% - 14%)	5% (0% - 12%)	30% (0% - 95%)	20.5% (0% - 72%)

Prior imatinib therapy and responses to imatinib are shown in Reviewer's Table A6 (Sponsor's Table 5.4.2).

Reviewer's Table A6. CA180002. Prior Imatinib Therapy: Imatinib-Resistant and Imatinib-Intolerant Subjects – All Treated Subjects

	Chronic QD N=21	**Chronic BID N=19**	**Accelerated N=11**	**Myeloid Blast N=23**	**Lymphoid Blast/Ph+ ALL, N=10**	**Total N=84**
Highest dose						
< 400 mg/day	0	0	0	0	0	0
400 – 600	6 (29%)	8 (42%)	4 (36%)	10 (43%)	3 (30%)	31 (37%)
> 600 mg/day	15 (71%)	11 (58%)	7 (64%)	13 (57%)	7 (70%)	
Length of imatinib Rx						
< 1 year	2 (10%)	2 (11%)	2 (18%)	7 (30%)	6 (60%)	19 (23%)
1 - 3 years	8 (38%)	6 (32%)	3 (27%)	7 (30%)	3 (30%)	27 (32%)
> 3 years	11 (52%)	11 (58%)	6 (55%)	9 (39%)	1 (10%)	38%)
Best hematologic response						
CHR	17 (81%)	13 (68%)	8 (73%)	15 (65%)	9 (90%)	62 (74%)
Best cytogenetic response						
CCyR	5 (24%)	1 (5%)	2 (18%)	2 (9%)	3 (30%)	13 (15%)
PCyR	6 (29%)	4 (21%)	2 (18%)	2 (9%)	0	14 (17%)
MCyR	11 (52%)	5 (26%)	4 (36%)	4 (17%)	3 (30%)	27 (32%)

Extent of Exposure: Extent of exposure is complex in this dose escalation study. The following Reviewer's Table A7 (Sponsor's Table 6.1) shows numbers of subjects accrued at each dose level in each disease phase.

Reviewer's Table A7. Number of Subjects Accrued in Each Dose Cohort by Disease Group

Starting dasatinib dose	Chronic QD N=21	Chronic BID N=19	Accelerated N=11	Myeloid Blast N=23	Ph+ ALL, N=10	Total N=84
15, 30, 50, 75, 105, 140, 180 mg QD	3 at each dose	-	-	-	-	21
25 mg BID	-	3	-	-	-	3
35 mg BID	-	7	-	-	1	7
50 mg BID	-	3	3	3	2	11
70 mg BID	-	6	3	11	3	26
90 mg BID	-	-	2	5	4	11
120 mg BID	-	-	3	4	-	7

Duration of Exposure by actual dosing days is shown in Reviewer's Table A8 (Sponsor's Table 6.1B). The majority of subjects with chronic phase CML received dasatinib for 6 months or longer. Most of the subjects in accelerated and blast phases received dasatinib for less than 6 months.

Reviewer's Table A8. CA180002. Duration of Exposure – Actual Dosing Days: All Treated Subjects

Duration of Exposure	Chronic QD N=21	Chronic BID N=19	Accelerated N=11	Myeloid Blast N=23	Ph+ ALL, N=10
Median no. of months (range)	11 (3 – 17.1)	6 (1.2 – 12.6)	3 (1.2 – 12.8)	4 (0.2 – 10.7)	3 (0.5 – 6.2)
<= 3 months	1 subject	2 subjects	6 subjects	10 subjects	5 subjects
> 3 - 6	2	7	1	8	4
> 6 – 12	9	8	3	5	1
> 12	9	2	1	0	0

The median dose in each dose cohort during each subject's entire time on treatment is shown in Reviewer's Table A9 (Sponsor's Table 6.1D).

Reviewer's Table A9. CA180002. Duration of Exposure – Doses In Actual Dosing Days, Entire Treatment Time: All Treated Subjects

Dose Cohort	Chronic QD N=21	Chronic BID N=19	Accelerated N=11	Myeloid Blast N=23	Ph+ ALL, N=10
15 mg QD	73 (56 -93)	-	-	-	-
30	47 (30-81)				
50	57 (50-91)				

75 105 140 180	94 (74-132) 112 (78-141) 140 (110-140) 180 (110-180)				
25 mg BID 35 50 70 90 120	-	31 (17-47) 35 (19-49) 50 (50-60) 67 (53-70) - -	- - 49 (38-55) 56 (51-70) 90 (90-90) 120 (120-120)	- - 50 (34-56) 70 (54-70) 90 (86-90) 120 (113-120)	- 34 (34-34) 50 (50-50) 70 (70-70) 89 (74-90) -
Total median (range)	93 (30-180)	49 (17-70)	70 (38-120)	70 (34-120)	70 (34-90)

Reviewer's Table A10 below shows dosing during all on study days. These data show median doses during the entire treatment period that includes dose interruptions. On the basis of these findings, the Sponsor concluded that dasatinib doses in the range of 35 – 70 mg BID represent the optimal balance between safety and efficacy according to the investigator's assessment of each individual subject.

Reviewer's Notes: Since doses were escalated to maximize efficacy within safety guidelines, chronic phase subjects appear to tolerate a QD dose of up to about 120 mg and a BID dose of up to about 50 mg; accelerated phase subjects, up to 90 mg BID; blast phase CML subjects, up to 120 mg BID; and Ph+ ALL subjects, up to 90 mg BID.

Reviewer's Table A10. CA180002. Duration of Exposure – Daily Doses During On-Study Period: All Treated Subjects

Dose Cohort	Chronic QD N=21	Chronic BID N=19	Accelerated N=11	Myeloid Blast N=23	Ph+ ALL, N=10
15 mg QD 30 50 75 105 140 180	63 (39 -82) 40 (23-59) 51 (38-71) 64 (60-126) 78 (48-114) 109 (82-125) 118 (51-155)	-	-	-	-
25 mg BID 35 50 70 90 120	-	26 (12-42) 24 (7-41) 36 (32-41) 52 (32-67) - -	- - 49 (31-55) 47 (14-70) 88 (86-90) 89 (88-120)	- - 50 (16-52) 53 (44-70) 83 (76-90) 120 (113-120)	- 27 (27-27) 50 (50-50) 70 (70-70) 89 (74-90) -
Total median (range)	64 (23-155)	35 (7-67)	70 (14-120)	67 (16-120)	70 (27-90)

Discontinuation of Study Therapy: Thirty-four subjects discontinued treatment as of May 31, 2005, the data cutoff date for the report. The reasons were: disease progression (22 subjects), death (7 subjects), allogeneic bone marrow transplant (3 subjects), second malignancy and withdrawal of consent (1 subject each).

Dose Modification: These data are not presented because of multiple dose escalations and regimen modifications.

Determination of MTD and Recommended Phase 2 Dose: This study was initially developed as a traditional Phase 1 study to assess short-term safety following a modified Fibonacci dose escalation scheme. However, once the activity of dasatinib was recognized, the study evolved into an efficacy and safety evaluation with permitted intra-subject dose escalation to optimize individual hematologic and cytogenetic responses.

The criteria for MTD were not met in any of the treatment groups. DLT was to be defined on the basis of adverse events attributed to dasatinib that occurred during the first 4 weeks of drug administration. The following events were considered to be DLTs (Reviewer's Table A11, data from Sponsor's Table 8.1):

Reviewer's Table A11. CA180002. Dose Limiting Toxicities

Disease phase	Dose levels administered	Subjects with DLT	DLT
Chronic	15, 30, 50, 75, 105, 140 and 180 mg QD	0/21	-
Chronic	25, 35, 50 and 70 mg BID	1/19	1/7 subjects at 35 mg BID: grade 4 thrombocytopenia in subject 2-208
Accelerated	50, 70, 90 and 120 mg BID	0/11	-
Myeloid Blast	50, 70, 90 and 120 mg BID	1/23	1/4 subjects at 120 mg BID: grade 3 pleural effusion and grade 4 pericardial effusion in subject 2-616
Lymphoid blast/Ph+ ALL	35, 50, 70 and 90 mg BID	0/10	-

The sponsor notes that the PK for subject 2-616 showed the highest exposure among all subjects in the trial. Among all 44 advanced phase subjects there were 17 subjects with pleural effusions, the majority of which (14) were grade 1 – 2 and managed with diuretics or interruption of dasatinib. There were 6 subjects with pericardial effusions in this population, 2 with grade 4 (subject 2-616, who had pneumonia and disease progression leading to death, and subject 1-504, who received a pericardial window and continued dasatinib at a reduced dose) and 4 with grade 1 - 2.

Efficacy: CHR and MCyR were observed in all phases of CML and in Ph+ ALL, as shown below in Reviewer's Table A12 (data from Sponsor's Tables 7.1A and 7.1B)

Reviewer's Table A12. CA180002. Cytogenetic and Hematologic Response Rates – All Treated Subjects

Response	Chronic QD N=21	Chronic BID N=19	Accelerated N=11	Myeloid Blast N=23	Lymphoid Blast/Ph+ ALL, N=10	Total N=84
MCyR ---CCyR ---PCyR	10 (48%) 10 0	8 (42%) 4 4	3 (27%) 2 1	8 (35%) 6 2	8 (80%) 3 5	37 (44%) 25 12
Confirmed CHR	20 (95%)	17 (90%)	6 (55%)	7 (30%)	5 (50%)	55 (65%)

The recommendation of phase 2 dose included efficacy analysis. The Sponsor noted that:

- Most of the subjects with CP CML (9 of 14) achieved CCyR at total daily doses of 100 – 140 mg, 1 subject at 50 mg, 3 subjects at 70 – 75 mg, and 1 subject at 180 mg. One subject in the 180 mg cohort achieved CCyR when the total daily dose was reduced to 105 mg. CHR was achieved at all dose levels, 15 – 180 mg QD and 25 – 70 mg BID.
- Among subjects with AP CML, CHR was achieved at all dose levels, ranging from 50 to 120 mg BID. CCyR was achieved by 1 subject at 70 mg BID and 1 subject at 120 mg BID.
- Among subjects with MB CML, CHR and NEL were achieved at all dose levels from 35 mg to 90 mg BID, but not at 120 mg BID. Most of CCyR were achieved at 70 mg BID dose (in 5 of 8 subjects). Two subjects achieved CCyR at 50 mg BID after de-escalating from 70 mg BID. On subject achieved CCyR at 90 mg BID dose. No subject achieved a MCyR at 120 mg BID.
- In summary, this trial was not designed to determine responses at each dose level and most of the subjects were treated with starting doses of 100 to 140 mg per day. Hematologic responses were noted in subjects taking 15 to 180 mg per day, and CCyR in most of the subjects occurred in subjects taking 100 to 140 mg per day.

Reviewer's Comments:
1. The following Reviewer's Table A13 shows the distribution of CHR and MCyR responses as a function of the dose at which each response occurred among the 84 subjects with all phases of CML and of Ph+ ALL. CHR and MCyR responses occurred either at starting dose or on escalation or on de-escalation.

Reviewer's Table A13. CA180002. Numbers of patients with CHR and MCyR as a Function of Dasatinib Dose in Study CA180002

Total daily dose (mg/day) QD and BID schedules	*CHR Responders/Total in Cohort*	*MCyR Responders/Total in Cohort*
15 mg	*1/3 (33%)*	*0/3 (0%)*
30 mg	*2/3 (67%)*	*1/3 (33%)*
50 mg	*7/6 (86%)*	*2/6 (33%)*
70 - 75 mg	*8/10 (80%)*	*3/10 (33%)*
100 – 105 mg	*12/14 (86%)*	*10/14 (71%)*
140 mg	*13/29 (45%)*	*13/29 (45%)*
180 mg	*5/14 (36%)*	*6/14 (43%)*
240 mg	*1/7 (14%)*	*1/7 (14%)*
Median	*100 – 105 mg/day*	*140 mg/day*

2. With respect to CHR, most of the responses (92%) occurred in the dose range of 50 mg to 180 mg; 69% of responses occurred with the dose range of 70 to 140 mg per day; and 52% of responses occurred with the dose range of 100 mg to 140 mg per day. (The percentages of patients in the above cohorts were 87%, 63%, and 51%, respectively.) The median dose was 100 – 105 mg per day. It should be noted that in most cases the responses were achieved with starting doses rather than as a result of dose escalation; thus, it is not known whether lower doses than 140 mg per day would have been equally efficacious.

3. With respect to MCyR, most of the responses (83%) occurred within the dose range of 100 mg to 180 mg per day; 66% of responses occurred within the dose range of 100 mg to 140 mg per day. (The percentages of patients in the 100 mg – 180 mg cohorts and in the 100 mg – 140 mg per day cohorts were 68% and 51%, respectively.) Again, since most of the responses with 100 mg per day and higher doses occurred in patients treated with these doses as starting doses and not as a result of escalation from lower doses, the doses required for MCyR may be lower.

4. Combining the dose-response data for both CHR and MCyR, the recommended starting dose appears to be about 100 mg per day (50 mg BID) with escalations as needed to 70 mg BID and to 90 mg BID.

5. Median doses at which MCyR and CHR were achieved in cohorts with each phase of CML and Ph+ ALL are shown in Tables A14 and A15 (data from Appendix 4.1.1 Hematologic Response, Appendix 4.2.3 Cytogenetic Response, and Appendix 5.1.1 Dosing).

Reviewer's Table A14. CA180002. Dosing in Subjects with MCyR (CCyR + PCyR)

Disease and Phase	Number of responders	Median dose (range)
Chronic phase CML, QD dosing	10	105 mg QD (15 – 180 mg QD)
Chronic CML phase, BID dosing	8	70 mg BID (35 – 70 mg BID)
Accelerated phase	3	90 mg BID (70 – 120 mg BID)
Myeloid blast phase	8	70 mg BID (50 – 90 mg BID)
Lymphoid blast CML	5	50 mg BID (25 – 90 mg BID)
Ph+ ALL	3	90 mg BID (70 – 90 mg BID)
Total	37	70 mg BID (15mg QD – 120 mg BID)

Reviewer's Table A15. CA180002. Dosing in Subjects with CHR

Disease and Phase	Number of responders	Median dose (range)
Chronic phase CML, QD dosing	20	90 mg QD (15 – 180 mg QD)
Chronic CML phase, BID dosing	17	50 mg BID (25 – 70 mg BID)
Accelerated phase	5	70 mg BID (50 – 120 mg BID)
Myeloid blast phase	3	70 mg BID (70 – 70 mg BID)
Lymphoid blast CML	2	80 mg BID (70 – 90 mg BID)
Ph+ ALL	1	70 mg BID
Total	48	70 mg BID (15mg QD – 120 mg BID)

The median effective doses may be lower for the following reasons: 1) many of higher doses (70, 90, and 120 mg BID) were starting doses, not escalated doses (therefore, it is not known whether treatment with lower doses may not be equally effective), and 2) higher doses were effectively lower than stated because of dose interruptions due to toxicity.

The data on starting doses and doses at which responses were achieved and on dose interruptions are shown in Tables A16 – A21.

In CP CML QD dosing, the median dose to achieve CHR was 105 mg. About 70% of all subjects who achieved CHR needed 105 mg QD or less. The median dose to achieve CyR was also 105 mg QD; 67% of subjects who achieved CyR needed 105 mg or less.

There were no dose interruptions when the starting dose was between 15 mg and 75 mg daily (the one exception was in subject 2-201 who had the dose held because of thrombocytopenia soon after starting on 15 mg dasatinib, but whose dose was escalated to 75 mg QD without further dose interruptions). However, most of the subjects (7/9) whose starting doses were between 105 mg and 180 mg daily had dose interruptions.

Reviewer's Table A16. CA180002. Starting Doses of Dasatinib and Dose Interruptions – CP CML, QD Dosing

Subject number	Dosing cohort Starting dose	Dose to achieve CHR	Dose to achieve MCyR	Dose interruptions due to toxicity before achieving CHR or MCyR or during maintenance
2-201	15 mg QD	15 mg QD	75 mg QD	Yes (1 episode only, after starting)
1-101	15 mg QD	50 mg QD	30 mg QD	No
1-102	15 mg QD	30 mg QD	105 mg QD	No
2-202	30 mg QD	30 mg QD	105 mg QD	No
1-103	30 mg QD	50 mg QD	-	No
2-203	30 mg QD	-	-	- (SAE when on 50 mg. D/C'd)
1-104	50 mg QD	50 mg QD	-	No
1-105	50 mg QD	50 mg QD	50 mg QD	No
2-205	50 mg QD	50 mg QD	105 mg QD	No
1-106	75 mg QD	105 mg QD	-	No
2-206	75 mg QD	105 mg QD	-	No
2-207	75 mg QD	105 mg QD	-	No
1-109	105 mg	75 mg QD	-	Yes
1-110	105 mg QD	105 mg QD	140 mg QD	Yes
2-209	105 mg QD	140 mg QD	-	Yes
1-112	140 mg QD	140 mg QD	-	Yes
2-211	140 mg QD	140 mg QD	140 mg QD	No
2-212	140 mg QD	105 mg QD	-	Yes
1-115	180 mg QD	180 mg QD	180 mg QD	Yes
1-116	180 mg QD	180 mg QD	-	No
2-216	180 mg QD	180 mg QD	105 mg QD	Yes

Reviewer's Table A17. CA180002. Starting Doses of Dasatinib and Dose Interruptions – CP CML, BID Dosing

Subject number	Dosing cohort Starting dose	Dose to achieve CHR	Dose to achieve MCyR	Dose interruptions due to toxicity before achieving CHR or CyR or during maintenance
1-107	25 mg BID	35 mg BID	-	No
1-108	25 mg BID	25 mg BID	-	Yes
2-204	25 mg BID	35 mg BID	35 mg BID	Yes
1-111	35 mg BID	35 mg BID	-	Yes
1-113	35 mg BID	35 mg BID	35 mg BID	No
1-114	35 mg BID	-	-	No (dose escalated to 70 mg BID w/o Response, D/C)
1-117	35 mg BID	35 mg BID	-	No
2-208	35 mg BID	-	-	Yes (interruptions due to toxicity on 35 and 25 mg BID. D/C)
2-210	35 mg BID	35 mg BID	-	No
2-213	35 mg BID	35 mg BID	50 mg BID	Yes
2-214	50 mg BID	50 mg BID	50 mg BID	No
1-118	50 mg BID	50 mg BID	-	Yes
2-215	50 mg BID	50 mg BID	-	Yes
2-219	70 mg BID	70 mg BID	70 mg BID	Yes
2-221	70 mg BID	70 mg BID	70 mg BID	Yes
1-119	70 mg BID	70 mg BID	-	Yes
1-120	70 mg BID	70 mg BID	70 mg BID	Yes
1-121	70 mg BID	50 mg BID	-	Yes
2-222	70 mg BID	70 mg BID	70 mg BID	Yes

The median dose to achieve CHR in the BID dosing cohorts was 50 mg BID. Twelve (12) of 17 subjects (71%) needed 50 mg BID or less. The median effective dose may be lower than 50 mg BID, because most of the subjects in the 70 mg BID starting dose cohort (5/6) achieved CHR at that dose. The median dose to achieve CyR was 60 mg BID, since one half of the subjects achieved CyR at 50 mg BID or lower and the other half at 70 mg BID. Dose interruptions due to toxicity occurred in all subjects treated with 70 mg BID, in 2 of 3 subjects treated with 50 mg BID, in 5 of 9 subjects treated with 35 mg BID, and in 1 subject treated with 25 mg BID.

The above data in CP CML patients suggest that it may be prudent to start dasatinib therapy with 35 mg BID dose and escalate to 50 mg BID and then to 70 mg BID. An alternative schedule would be a 105 mg QD starting dose with escalation to 140 mg QD.

Reviewer's Table A18. CA180002. Starting Doses of Dasatinib and Dose Interruptions – AP CML

Subject number	Dosing cohort Starting dose	Dose to achieve CHR	Dose to achieve MCyR	Dose interruptions due to toxicity before achieving CHR or MCyR or during maintenance
1-503	50 mg BID	50 mg BID	-	No (Yes, when escalated to 70 mg BID)
1-505	50 mg BID	50 mg BID	-	Yes
1-508	50 mg BID	-	- (Unable to det.)	No
1-511	70 mg BID	70 mg BID	50 mg BID	Yes (on 70 and 50 mg BID)
1-514	70 mg BID	-	-	Yes (on 70, 50, and 35 mg BID)
1-517	70 mg BID	-	- (Unable to det.)	No
2-607	90 mg BID	90 mg BID	90 mg BID	No
2-608	90 mg BID	-	- (Unable to det.)	No
2-613	120 mg BID	-	-	Yes
2-615	120 mg BID	-	120 mg BID	Yes
2-618	120 mg BID	120 mg BID	-	Yes

In AP CML cohorts CHR was achieved in 50 mg, 70 mg, 90 mg, and 120 mg BID cohorts, suggesting that patients could be started at 50 mg BID and escalated as needed.

Reviewer's Table A19. CA180002. Starting Doses of Dasatinib and Dose Interruptions – MB CML

Subject number	Dosing cohort Starting dose	Dose to achieve CHR	Dose to achieve MCyR	Dose interruptions due to toxicity before achieving CHR or MCyR or during maintenance
1-504	50 mg BID	-	-	Yes (at 50, 35, and 25 mg BID)
1-518	50 mg BID	-	-	Yes
2-601	50 mg BID	-	-	No
1-507	70 mg BID	-	-	Yes
1-509	70 mg BID	-	70 mg BID	No
1-510	70 mg BID	-	-	No
1-512	70 mg BID	70 mg BID	70 mg BID	Yes

1-513	70 mg BID	-	-	Yes
1-515	70 mg BID	-	70 mg BID	No
1-516	70 mg BID	50 mg BID	50 mg BID	Yes (70 mg BID)
1-525	70 mg BID	-	50 mg BID	Yes (70 mg and 35 mg BID)
2-602	70 mg BID	70 mg BID	70 mg BID	No
2-603	70 mg BID	-	70 mg BID	No
1-519	90 mg BID	-	-	Yes
1-520	90 mg BID	-	(Unable to det.)	Yes
1-521	90 mg BID	-	-	Yes
2-610	90 mg BID	-	-	Yes
2-611	90 mg BID	-	-	No
2-614	90 mg BID	-	90 mg BID	Yes
1-523	120 mg BID	-	(Unable to det.)	No (short course)
1-524	120 mg BID	-	-	No (short course)
2-616	120 mg BID	-	(Unable to det.)	No (short course)
2-619	120 mg BID	-	(Unable to det.)	No (short course)

There were no CHR or MCyR responses with 50 mg BID starting dose in MB CML. Most of the responses occurred with 70 mg BID starting dose; 2 patients achieved responses on de-escalation to 50 mg BID. There was only one MCyR and no CHRs among the 10 patients in the 90 mg BID and 120 mg BID cohorts. These data support 70 mg BID was the appropriate starting dose in MB CML. One-half of the patients had dose interruptions with this dose.

Reviewer's Table A20. CA180002. Starting Doses of Dasatinib and Dose Interruptions – LB CML

Subject number	Dosing cohort Starting dose	Dose to achieve CHR	Dose to achieve MCyR	Dose interruptions due to toxicity before achieving CHR or MCyR or during maintenance
1-506	35 mg BID	-	25 mg BID	Yes
1-501	50 mg BID	-	50 mg BID	No
1-502	50 mg BID	-	50 mg BID	No
2-605	70 mg BID	70 mg BID	70 mg BID	Yes
2-612	90 mg BID	90 mg BID	90 mg BID	No

In LB CML, CHRs were achieved in only 2 patients who were treated with 70 mg and 90 mg BID; MCyRs were achieved in patients treated with 25 mg, 50 mg, 70 mg, and 90 mg BID. A 50 mg BID starting dose may be appropriate.

Reviewer's Table A21. CA180002. Starting Doses of Dasatinib and Dose Interruptions – Ph+ ALL

Subject number	Dosing cohort Starting dose	Dose to achieve CHR	Dose to achieve MCyR	Dose interruptions due to toxicity before achieving CHR or MCyR or during maintenance
2-604	70 mg BID	70 mg BID	70 mg BID	No
1-522	90 mg BID	-	90 mg BID	No (1 mo. course)
2-606	90 mg BID	-	90 mg BID	No
2-609	90 mg BID	-	-	No
2-620	90 mg BID	-	-	No (14 day course)

In Ph+ ALL patients, one CHR occurred with a 70 mg BID dose, and MCyRs with 70 mg BID and 90 mg BID doses. A 70 mg BID starting dose may be appropriate.

Responses in imatinib intolerant and imatinib-resistant subjects. The Sponsor carried out analyses of cytogenetic and hematologic response rates in imatinib-intolerant and imatinib-resistant subjects. Reviewer's Table A22 summarizes the cytogenetic response data and Reviewer's Table A23 summarizes the hematologic response data in imatinib-intolerant and imatinib-resistant subjects (data are assembled from Sponsor's tables under each disease and disease phase).

Reviewer's Table A22. CA180002. MCyR Rates in Imatinib-intolerant and Imatinib-resistant Subjects

Disease Phase	Imatinib-intolerant	Imatinib-resistant	Total
Chronic QD	3/4 (75%)	7/17 (41%)	10/21 (48%)
Chronic BID	3/4 (75%)	5/15 (33%)	8/19 (42%)
Accelerated	1/4 (25%)	2/7 (29%)	3/11 (27%)
Myeloid Blast	0/1 (0%)	8/22 (36%)	8/23 (35%)
Lymphoid/Ph+ ALL	1/1 (100%)	7/9 (78%)	8/10 (80%)
Total	8/14 (57%)	29/70 (41%)	37/84 (44%)

Reviewer's Table A23. CA180002. CHR Rates in Imatinib-intolerant and Imatinib-resistant Subjects

Disease Phase	Imatinib-intolerant	Imatinib-resistant	Total
Chronic QD	4/4 (100%)	16/17 (94%)	20/21 (95%)
Chronic BID	4/4 (100%)	13/15 (87%)	17/19 (89%)
Accelerated	1/4 (25%)	4/7 (57%)	5/11 (45%)
Myeloid Blast	0/1 (0%)	3/22 (14%)	3/23 (13%)
Lymphoid blast CML/Ph+ ALL	1/1 (100%)	3/9 (33%)	4/10 (40%)
Total	10/14 (71%)	39/70 (56%)	49/84 (58%)

Comments:

- The number of imatinib-intolerant subjects is small, but the results suggest that the response rates in the imatinib-intolerant may be higher than in the imatinib-resistant populations.
- Hematologic response rates were higher than cytogenetic response rates in chronic phase CML and in accelerated phase CML.
- Cytogenetic response rates were higher than hematologic response rates in myeloid blast CML, lymphoid blast CML and Ph+ ALL.

Reviewer's Conclusions:

- A recommended starting dose on the basis of safety could not be established.
- There is no linear dose-response relationship with MCyR and CHR endpoints. Most of the responses occurred with 50 mg BID and 70 mg BID doses. Responses occurred at lower doses than 50 mg BID and with higher doses than 70 mg BID, but were less frequent.
- The recommended starting dose for CP CML patients is about 50 mg BID, with dose escalations/de-escalations as needed.
- Once daily or BID dosing results in the same response rates in CP CML patients.
- The recommended starting dose for AP CML, MB CML, LB CML and Ph+ ALL patients is 70 mg BID.
- Imatinib intolerant patients appear to have higher response rates than imatinib-resistant patients.

10.1.2 Chronic CML. CA180013: A Phase 2 Study to Determine the Activity of BMS-354825 in Subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have Disease that is Resistant to High Dose Imatinib Mesylate (Gleevec®) or who are Intolerant of Imatinib.

Study Status: The study was started on February 4, 2005 and is ongoing. Efficacy (and Cumulative Safety) is described for all subjects enrolled on or before May 12, 2005 and treated on or before May 31, 2005. Two hundred one (201) were enrolled at 41 centers worldwide and 186 subjects were treated at 39 centers. (A total of 424 subjects were enrolled by July 15, 2005,

when accrual was closed.) The submitted interim report is based on an interim analysis performed on these treated 186 subjects who had a minimum of 3 months of follow-up.

Study Objectives:
The primary objective was to estimate the MCyR rate to dasatinib in subjects with chronic phase CML who had imatinib-resistant disease.
The secondary objectives were:

- To estimate the MCyR rate in imatinib-intolerant subjects.
- To assess the durability of MCyR and time to MCyR in the imatinib-resistant and the imatinib-intolerant groups.
- To estimate the CHR rate, duration of CHR, and time to CHR in the imatinib-resistant and the imatinib-intolerant groups.
- To assess the safety and tolerability of dasatinib.
- To assess the health-related QoL using FACT-G.
- To estimate the major molecular response rate in the imatinib-resistant and the imatinib-intolerant groups.
- To collect blood samples for population PK analysis.

Study Design: Open-label, multicenter Phase 2 study of dasatinib in subjects with chronic phase CML resistant to imatinib (> 600 mg/day or ≤ 600 mg/day with mutations of the BCR-ABL gene) or who were intolerant of imatinib at any dose. Dasatinib dose was 70 mg BID. Dose escalation to 90 mg BID was allowed for subjects with disease progression or lack of response. Up to 2 dose reductions were allowed for toxicity. Treatment continued until disease progression or intolerable toxicity or withdrawal from the study. The primary efficacy endpoint was the rate of MCyR. Cytogenetic response was evaluated every 12 weeks. All subjects were followed for at least 30 days after the last dasatinib dose or after recovery from all toxic effects.

Primary efficacy endpoint: MCyR at 12 weeks.
Secondary efficacy endpoints: Durability and time to MCyR; rate of CHR, duration of CHR, and time to CHR.

Study Population
Key Inclusion Criteria:

- Men and women, at least 18 years of age, who signed informed consent.
- Have chronic phase CML, defined as < 15% blasts in peripheral blood and in bone marrow, < 20% basophils in peripheral blood, < 30% blasts + promyelocytes in peripheral blood and bone marrow, platelets ≥ 100,000/mm^3 unless thrombocytopenic due to recent therapy, no extramedullary involvement (other than liver or spleen).
- Developed progressive disease while being treated with imatinib > 600 mg/day with acquired or primary resistance.
- Acquired resistance was defined as progression after achieving MCyR or CHR on imatinib at any dose, manifested by 1) after achieving MCyR, lost MCyR and had a ≥ 30% increase in Ph+ metaphases on 2 analyses 4 or more weeks apart while receiving imatinib, or 2) after achieving a confirmed CHR lost CHR over a 2 week period while receiving imatinib, or 3) after failing to achieve a confirmed CHR on maximal doses had

a doubling of WBC to > 20,000/mm³ or by an increase by > 50,000/mm³ on 2 occasions at least 2 weeks apart.

- Primary resistance was defined as failure to achieve 1) MCyR after 12 months, or 2) CyR after 6 months, or 3) CHR after 3 months at any dose, or 4) continuously increasing WBC on at least 2 consecutive evaluations at least 2 weeks apart with a doubling of WBC to > 20,000/mm³ or by an increase by > 50,000/mm³ above nadir after starting imatinib.
- Resistance to imatinib ≤ 600 mg/day with genetic mutation in the BCR-ABL gene associated with a high level of resistance (list provided).
- Intolerance of imatinib at any dose. Subjects intolerant to 800 mg/day must have demonstrated PD or lack of CyR at 600 mg or lower doses. Intolerance was defined as imatinib-related Grade ≥ 3 non-hematological toxicity or Grade 4 hematological toxicity lasting > 7 days.

Key Exclusion Criteria:

- Eligible and willing to undergo transplantation during the screening period.
- Women of childbearing potential who were unwilling or unable to use an acceptable method of pregnancy avoidance for the entire study period of at least 1 month before and for at least 3 months after completion of the study medication.
- Pregnancy, positive pregnancy test on enrollment or prior to study drug administration, or breastfeeding.
- Men whose partners are women of childbearing potential unwilling or unable to use pregnancy avoidance methods for the periods stated above.
- Subjects who have previously described BCR-ABL mutation (a list of mutation is provided).
- Previous accelerated phase or blast crisis CML.
- Intolerance to imatinib: Grade ≥ 3 imatinib-related non-hematological toxicity, Grade 4 imatinib-related hematological toxicity lasting > 7 days, and imatinib-related toxicity that leads to imatinib discontinuation or disruption in dosing > 4 weeks.
- Uncontrolled or significant cardiovascular disease, significant bleeding disorder unrelated to CML, and concurrent incurable malignancy other than CML.

Treatments Administered

Dasatinib was administered at a dose of 70 mg BID. Dose escalation and dose modifications (interruption, de-escalation, and discontinuation) were as described in CA180017, except that failure to achieve CHR after 8 weeks of therapy also triggered dose escalation to 90 mg BID.

Concomitant Treatments

Anagrelide for platelet counts > 700,000/mm³, hydroxyurea for WBC > 50,000/mm³, CSF and erythropoietin permitted. Medications associated with QT prolongation, with platelet function inhibition, and anticoagulants prohibited. CYP3A4 substrates, inhibitors, and inducers were, if possible, avoided.

Protocol Deviations

Of the 186 eligible subjects, 33 (18%) had one or more protocol deviation:

- 29 (16%) were missing at least one of the baseline hematology or bone marrow results required for eligibility, such as no differential, or inadequate or unavailable bone marrow sample. Five subjects had < 100,000 platelets/mm³.

- Five had no Ph+ metaphases. Ph+ status was confirmed by FISH (fluorescent in situ hybridization) in 2 of these subjects. One subject had no Ph+ metaphases and did not meet the criteria for chronic phase CML.

These results are shown in Reviewer's Table A24.

Reviewer's Table A24. CA180013. Significant Protocol Deviations – All Treated Subjects

	Imatinib Intolerant N = 59	**Imatinib Resistant N = 127**	**Total N = 186**
No deviations	49 (83%)	104 (82%)	153 (82%)
No Ph+ chromosome	4 (7%)	1 (1%)	5 (3%)
Chronic phase Ph+ CML criteria not met	8 (14%)	21 (17%)	29 (16%)

Disposition of Study Subjects

Of the 201 subjects enrolled in the study, 186 were treated, 12 were not treated (10 did not meet a variety of study entry criteria, one withdrew consent, and one had an AE before treatment), and 3 started treatment after closing date for the first dose.

Subject disposition of all treated subjects is shown in Reviewer's Table A25.

Reviewer's Table A25. CA180013. Subject Disposition – All Treated Subjects With Minimum Follow-up of 6 Months

	Imatinib Intolerant N = 59	**Imatinib Resistant N = 127**	**Total N = 186**
On Treatment – Min. 3-Months Follow-up Analysis	55 (93%)	109 (86%)	164 (88%)
On Treatment- Min. 6 Months Follow-up Analysis	55 (93%)	105 (83%)	160 (86%)
Off Treatment	4 (7%)	22 (17%)	22 (12%)
- Disease Progression	0	6 (5%)	4 (2%)
- Dasatinib toxicity	2 (3%)	9 (7%)	9 (5%)
- Dasatinib-related AE	1 (2%)	2 (2%)	3 (2%)
- Subject request	1 (2%)	2 (2%)	3 (2%)
- Death	0	2 (2%)	2 (1%)
- Other	0	1 (1%)	1 (1%)

Data Sets Analyzed

- All treated subjects (all subjects who were enrolled by 5/12/05 and who received at least one dose of dasatinib by 5/31/05): 186 subjects.
- Evaluable for cytogenetic response (all treated subjects who have at least one on-study valid cytogenetic assessment [i.e. more than 0 metaphases have been observed] or subjects who discontinued for any reason prior to the first on-study valid cytogenetic assessment): 169 subjects.
- Evaluable for cytogenetic response based on ≥ 20 metaphases (all treated subjects who have at least one on-study valid cytogenetic assessment where ≥ 20 metaphases have been observed or subjects who discontinued for any reason prior to the first on-study valid cytogenetic assessment): 151 subjects.

Demographic and Baseline Characteristics

Reviewer's Table A26. CA180013. Demographic Characteristics – All Treated Subjects

Characteristic	Intolerant, N = 59	Resistant, N = 127	Total, N = 186
Age, years			
Mean ± SD	56.0 ± 12.1	56.7 ± 12.6	56.5 ± 12.4
Median	59.0	59.0	59.0
21-45 years	12 (20%)	31 (24%)	43 (23%)
46-65	35 (59%)	59 (47%)	94 (51%)
66-75	10 (17%)	33 (26%)	43 (23%)
> 75	2 (3%)	4 (3%)	6 (3%)
Gender			
Male	26 (44%)	60 (47%)	86 (46%)
Female	33 (56%)	67 (53%)	100 (54%)
Race			
White	56 (95%)	117 (92%)	173 (93%)
Black/African American	1 (2%)	7 (6%)	8 (4.3%)
Asian	1 (2%)	2 (2%)	3 (2%)
Other	1 (2%)	1 (1%)	2 (1%)
ECOG PS			
0	42 (72%)	94 (74%)	136 (73%)
1	17 (29%)	31 (24%)	48 (26%)
Not reported	0	2 (2%)	2 (1%)

CML History

CML history for imatinib-resistant and imatinib-intolerant subjects is summarized in Reviewer's Table A27 below. Resistance was defined as acquired or primary at the maximum tolerated dose of imatinib or secondary to a mutation associated with imatinib resistance. The reasons for imatinib intolerance in 59 subjects were Grade 3 or 4 rash (22 subjects), hepatotoxicity/elevated LFTs (17), musculoskeletal symptoms (13), Grade 3 or 4 hematologic toxicity (10), Grade 3 or 4

GI toxicity (6), edema (5), Grade 3 or 4 pulmonary toxicity (3), Grade 3 or 4 fatigue (2), weight gain (2), renal failure (1), and anaphylaxis (1).

There were marked differences in disease histories between the imatinib-intolerant and imatinib-resistant groups, as listed below.

1) The median time from the initial diagnosis of CML to entry into the study was much shorter in the intolerant group than in the resistant group (26 months vs. 78 months), as was the median length of imatinib therapy (54% vs. 5% of subjects were treated for less than 1 year).
2) Subjects in the resistant group had on the average a greater number and types of previous therapies for CML than subjects in the intolerant group.
3) The highest imatinib dose with which patients had been treated was lower in the imatinib-intolerant than in the imatinib-resistant population (8% vs. 72% of subjects were treated with > 600 mg/day).
4) A greater percentage of subjects had achieved CHR in the imatinib-resistant group than in the imatinib-intolerant group (91% vs. 76%).
5) Conversely, a greater percentage of subjects had achieved CCyR in the imatinib- intolerant group than in the imatinib-resistant group (24% vs. 14%).

Reviewer's Table A27. CA180013. Baseline CML History Characteristics

Characteristic	**Imatinib-intolerant N = 59**	**Imatinib-resistant N = 127**	**Total N = 186**
Time from initial CML diagnosis Median (min – max), (months)	26.3 (4.4 – 144.5)	77.6 (4.1 – 250.5)	63.8 (4.1 – 250.5)
Length of imatinib therapy No. of subjects (%)			
< 1 year	32 (54.2%)	6 (5%)	38 (20%)
1 – 3 years	18 (31%)	30 (24%)	48 (26%)
> 3 years	9 (15%)	91 (72%)	100 (54%)
Highest dose			
400 – 600 mg/day	54 (92%)	35 (28%)	89 (48%)
> 600 mg/day	5 (8%)	92 (72%)	97 (52%)
Best hematologic response to imatinib			
CHR	45 (76%)	115 (91%)	160 (86%)
Stable	7 (12%)	7 (6%)	14 (8%)
Progression	0	3 (2%)	3 (2%)
Undetermined/unreported	7 (12%)	2 (2%)	9 (5%)
Best cytogenetic response to imatinib			
CCyR	14 (24%)	18 (14%)	32 (17%)
PCyR	10 (17%)	20 (16%)	30 (16%)
Other	34 (58%)	89 (70%)	123 (66%)
Not reported	1 (2%)	0	1 (<1%)

Previous other therapy No. of subjects (%)			
Bone marrow transplant	4 (7%)	13 (10%)	17 (9%)
Radiotherapy	1 (2%)	2 (2%)	3 (2%)
Chemotherapy	15 (25%)	64 (50%)	79 (43%)
Interferon	32 (54%)	98 (77%)	130 (70%)
Hydroxyurea or anagrelide	44 (75%)	115 (91%)	159 (86%)

Baseline Hematologic Disease Status

Baseline peripheral blood counts are summarized in Reviewer's Table A28. The lowest WBC of 400/mm³ was recorded in a patient on treatment with hydroxyurea (the subject's WBC was 22,000/mm³ one week before). Likewise, the lowest platelet count of 24,000/mm³ occurred in a patient on treatment with hydroxyurea. The sponsor notes that 80 – 90% of subjects had normal WBC, neutrophil, and platelet counts, and 85% of subjects had Grade 0 – 1 baseline Hgb. Eleven subjects (6%) had splenic involvement and one of them had liver involvement.

Reviewer's Table A28. CA180013. Baseline Hematologic Disease Status

Characteristic	**Imatinib-intolerant** **N = 59**	**Imatinib-resistant** **N = 127**
WBC median (min – max) < 20,000/mm³ ≥ 20,000/mm³	7,400/mm³ (2,000 – 182,700) 51 subjects (86%) 8 subjects (14%)	11,700/mm³ (400 – 196,500) 78 subjects (61%) 48 subjects (38%)
Basophils in PB No. of subjects (%) Median (min – max)	 43 (73%) 1% (0% – 19%)	 84 (66%) 3% (0% – 18%)
Platelet count, median (min – max)	254,000/mm³ (61,000 – 1,165,000)	299,500/mm³ (24,000 – 1,912,000)
Hgb, median (min – max)	13.2 g/dL (8.3 – 16.0)	11.7 g/dL (6.5 – 15.5)
Involvement of spleen, liver, nodes, other organs	0	11 spleen, 1 liver & spleen

Extent of Exposure

Data on the dose intensity and duration of treatment is available in the original submission, but no in the 6-month Efficacy Summary. The average daily dose of 114 mg/day is about 19% lower than the target dose of 140 mg/day. About 25% of all patients had been treated for 3 months or less. These data are summarized in Reviewer's Table A29.

Reviewer's Table A29. CA180013. Dose Intensity and Duration of Treatment

	Imatinib intolerant N = 59	**Imatinib-resistant N = 127**	**Total 186**
Daily dose, median (min – max)	113.0 (56.0 – 141.0)	115.0 (19.0 – 170.0)	114.0 (19.0 – 170.0)
% of dose administered			
< 90%	32 patients (54%)	79 (62%)	111 (60%)
> 90 -100%	25 (42%)	43 (34%)	68 (37%)
> 100%	2 (3%)	5 (4%)	7 (4%)
Duration of treatment, months			
Median (min – max)	3.71 (0.03 – 6.44)	3.98 (0.03 – 7.36)	3.85 (0.03 – 7.36)
Patients treated for			
≤ 3 months	14 patients (24%)	34 patients (27%)	48 (26%)
3 – 6 months	42 (71%)	79 (62%)	121 (65%)
> 6 months	3 (5%)	14 (11%)	17 (9%)

Discontinuation of Study Therapy (Minimum Follow-up of 6 Months data)

Twenty-six (26) subjects discontinued from the study (4 imatinib-intolerant and 18 imatinib-resistant) by the minimum 6-month follow-up period for the following reasons:

- Dasatinib toxicity (11): one case each of Grade 2 neuropathy, ventricular dysfunction, pleural effusion and or without pneumonia, pyoderma gangrenosum, pulmonary edema, erythema, thrombocytopenia, and anemia
- Disease progression (6)
- AEs considered unrelated to dasatinib (3): one patient each with prolonged QTc, atrial fibrillation, and bone pain
- Deaths (2): CNS hemorrhage, and renal failure
- Withdrawal of consent (3)
- Non-compliance (1).

Twenty-two (22) subjects discontinued from the study during the 3-month follow-up. The additional 4 patients discontinued during the following 3 months, 2 because of dasatinib toxicity and 2 because of disease progression.

Dose Reductions, Interruptions, and Escalations (Interim Report data)

Most of the subjects (79%) required dose interruptions and 52% required dose reductions. The main reason for dose reduction/interruption was myelosuppression (31% subjects had dose reduced, 43% had dose interrupted due to hematological toxicity). Dose modifications due to non-hematological toxicity occurred for a variety reasons. The median time to first dose reduction/interruption due to toxicity was 29 days (range 2 – 179). The median length of first interruption due to toxicity was 14 days (range 1 – 61 days). Only 6 subjects (3%) had dose escalated to 90 mg BID.

Efficacy Results

Primary Efficacy Endpoint: Cytogenetic Response (Minimum Follow-up of 6 Months data)

Dasatinib treatment resulted in high cytogenetic response rates, especially in the imatinib-intolerant population. The MCyR rate was 73% in the imatinib-intolerant subjects and 31% in the imatinib-resistant subjects. CCyR rate 56% in the imatinib-intolerant subjects and 22% in the imatinib-resistant subjects.

The 42% percentage point difference in MCyR response rates between the intolerant and resistant populations is striking. The average MCyR for both subject populations combined was 45%.

Absence of responses and minor and minimal responses were more frequent in the resistant population than in the intolerant population.

Reviewer's Table A30. CA180013. Cytogenetic Response – All Treated Subjects

Response	**Imatinib-intolerant, N = 59**	**Imatinib-resistant N = 127**	**Total N = 186**
MCyR (CCyR + PCyR)	43 (73%)	40 (31%)	83 (45%)
---Complete (0% Ph+)	33 (56%)	28 (22%)	61 (33%)
---Partial (>0% - 35% Ph+)	10 (17%)	12 (9%)	22 (12%)

Analysis of cytogenetic response in Evaluable subjects (6-month follow-up data) is shown in Reviewer's Table A31 below. The response rates are higher (MCyR of 80% in the imatinib-intolerant subjects and of 33% in the imatinib-resistant subjects), because some of the subjects in the "unable to determine" category were omitted for reasons described above in Population Data Sets.

Reviewer's Table A31. CA180013. Cytogenetic Response – Evaluable Subjects

Response	**Imatinib-intolerant, N = 54**	**Imatinib-resistant N = 120**	**Total N = 174**
MCyR (CCyR + PCyR)	43 (80%)	40 (33%)	83 (48%)
---Complete (0% Ph+)	33 (61%)	28 (23%)	61 (35%)
---Partial (>0% - 35% Ph+)	10 (19%)	12 (10%)	22 (13%)

The response rates in evaluable subjects who had ≥ 20 metaphases are shown in Reviewer's Table A32 below.

Reviewer's Table A32. CA180013. Cytogenetic Response – Evaluable Subjects with ≥ 20 Metaphases

Response	Imatinib-intolerant, N = 59	Imatinib-resistant N = 127	Total N = 186
MCyR (CCyR + PCyR)	42 (71%)	33 (26%)	75 (40%)
Complete (0% Ph+)	33 (56%)	24 (19%)	57 (31%)
Partial (>0% - 35% Ph+)	9 (15%)	9 (7%)	18 (10%)

Six subjects had their dasatinib dose escalated to 90 mg BID because of disease progression or lack of CyR. Two had a minimal CyR, 3 had no CyR, and CyR could not be evaluated in 1 subject.

Reviewer's Note: The imatinib-intolerant population may be similar to an imatinib-naive population and has a high response rate. The much lower response rate in the imatinib-resistant population suggests that imatinib resistance extends in part to dasatinib.

Secondary Efficacy Endpoints: Time to MCyR and Duration of MCyR

The median time to MCyR was 85 days, as shown in Figure A1 (Sponsor's Supplemental Figure S.4.2) below. It should be noted that cytogenetic analyses were carried out, according to protocol, after 12 weeks or 84 days of treatment. The duration of MCyR could not be determined because all 83 subjects with MCyR remained alive and in response at the time of data cutoff (Figure A2). The maximum duration at the time of 6-month data cutoff is 4.7+ months.

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Figure A1. Time to MCyR

Figure S.4.2:
Time to MCyR in Resistant and Intolerant Subjects

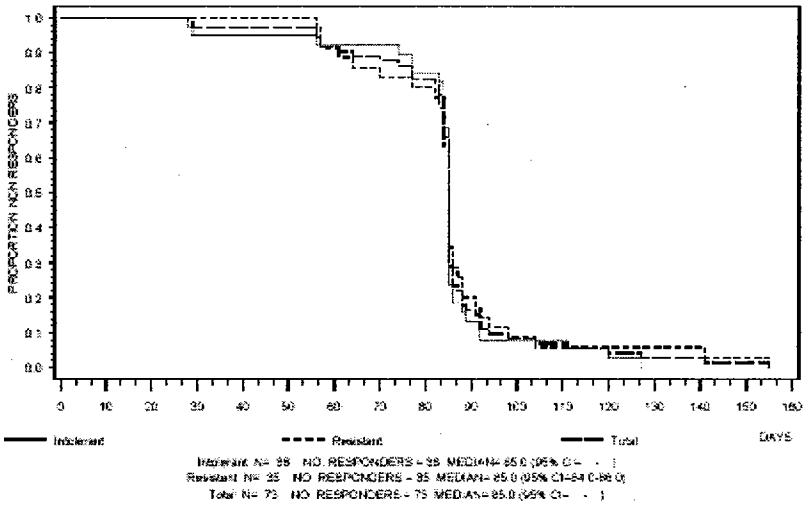

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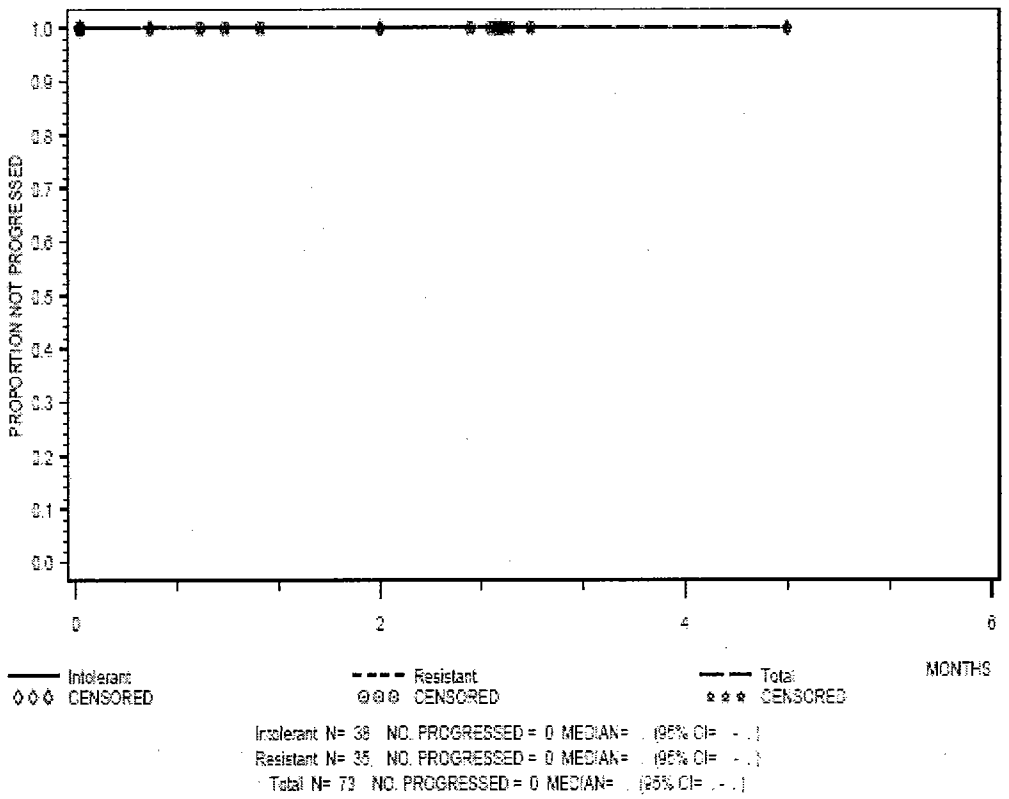
Figure A2. Duration of MCyR

Figure 7.2: Duration of MCyR in Resistant and Intolerant Subjects



Secondary Endpoint: Complete Hematologic Response (CHR)

At baseline, 31/59 (53%) imatinib-intolerant subjects and 41/127 (32%) imatinib-resistant subjects had normal peripheral blood counts. They were eligible for inclusion into the study because of cytogenetic and/or hematologic progression on imatinib or a mutation associated with imatinib resistance. The CHR rate for these subjects, for subjects with abnormal peripheral blood counts at baseline, and for both populations are shown in Reviewer's Table A33. Subjects with abnormal peripheral blood counts, especially if they are imatinib-resistant, appear to have lower response rates than subjects with normal counts.

Reviewer's Table A33. CA180013. Complete Hematologic Response

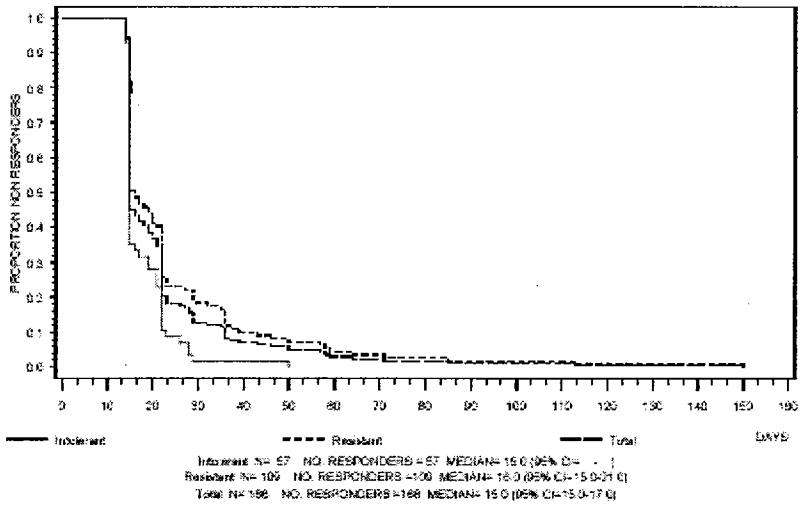
	No. of subjects (%) with CHR/Treated Imatinib-intolerant N = 59	**No. of subjects (%) with CHR/Treated Imatinib-resistant N = 127**	**Total N = 186**
All subjects	57/59 (97%)	111/127 (87%)	168/186 (90%)
Abnormal blood counts at baseline	26/28 (93%)	70/86 (81%)	96/109 (84%)
Normal blood counts at baseline	31/31 (100%)	39/41 (95%)	70/72 (97%)

Secondary Efficacy Endpoints: Time to CCR and Duration of CCR

The median time to CHR was 16 days (CHR could only begin 14 days after the start of treatment), as shown in Figure A3 (Sponsor's Figure S.4.1) below.

Figure A3. Time to CHR in CP CML

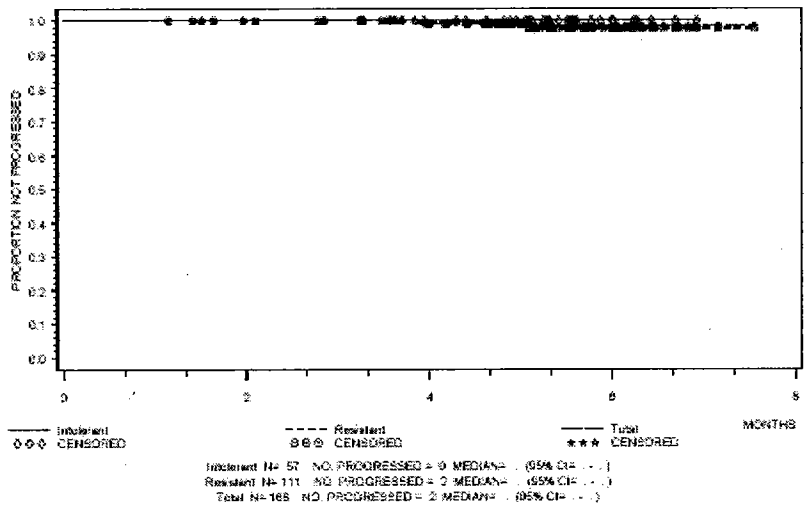
Figure S.4.1:
Time to CHR in Resistant and Intolerant Subjects



The longest duration of response has been 7.6+ months, the shortest, 1.1+ months (Figure A4, Sponsor's Figure 3.2A). Among those subjects who had achieved CHR, 2 of the 111 imatinib-resistant subjects had progressed, one after 5.1 months of therapy, the other after 3.9 months.

Figure A4. Duration of CHR in CP CML

Figure 3.2A: Duration of CHR (Study CA180013)



Extramedullary Disease

Eleven imatinib-resistant subjects had extramedullary involvement at baseline (spleen in 10 subjects, liver and spleen in 1 subject). Eight of these subjects (73%), including the one with liver involvement at baseline, achieved resolution of their extramedullary disease after treatment with dasatinib.

Reviewer's Conclusions:

- Dasatinib 70 mg BID treatment resulted in about 45% of patients achieving a MCyR (33% CCyR and 12% PCyR).
- Most patients achieved MCyR after 12 weeks of treatment.
- MCyR was durable, as all patients maintained MCyR during the minimum 6-month follow-up.
- MCyR rate was higher among imatinib intolerant patients than among imatinib-resistant patients (73% vs. 31%).
- About 90% of patients achieved CHR (97% imatinib intolerant and 87%, imatinib resistant). The median time to CHR was 16 days and the median duration of response was 7.6+ months.

10.1.3 Accelerated Phase CML. CA180005: A Phase 2 Study of Dasatinib (BMS-354825) in Subjects with Accelerated Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate

Study Status: The study was started on December 6, 2004 and is ongoing. Accrual was closed on July 12, 2005 with 197 subjects enrolled. The submission contains data on the first 120 enrolled subjects (enrollment cutoff date of May 12, 2005) of whom 107 were treated (first dose received

by May 22, 2005). The subject population included 99 imatinib-resistant and 8 imatinib-intolerant subjects. Subjects were enrolled in 40 centers worldwide. The submitted report is based on interim analysis of the minimum 3-month follow-up data (data cutoff was October 19, 2005) and on follow-up analysis with a data cutoff date of November 10, 2005.

Study Objectives:
Primary Objective: To estimate the major hematologic response (MaHR) and overall hematologic response (OHR) rates to dasatinib in accelerated phase CML subjects with primary or acquired resistance to imatinib.

Secondary Objectives:

- To assess the durability of hematologic response and time to hematologic response in the imatinib-resistant and imatinib-intolerant groups.
- To assess hematologic, cytogenetic, and molecular responses in the imatinib-intolerant group.
- To measure health-related Q of L using the FACT-G questionnaire.
- To assess further the safety and tolerability of dasatinib.

Study Design: Open-label, multicenter Phase 2 study in subjects with accelerated phase CML with primary and acquired resistance to imatinib. A separate group of imatinib-intolerant subjects was also enrolled. Dasatinib dose was 70 mg BID. Treatment continued until disease progression or development of intolerable toxicity. Dose modifications were allowed for disease progression (dose increased to 100 mg BID) or toxicity (2 dose reductions, to 50 mg BID, then to 40 mg BID). Subjects were followed for a minimum of 30 days after the last dasatinib dose or until recovery from toxicity.

Study Population
Key Inclusion Criteria:

- Men and women, at least 18 years of age, who signed informed consent.
- Ph+ (or BCR-ABL) accelerated phase CML defined as manifesting at least one of the following: 1) 15% to <30% blasts in peripheral blood (PB) or bone marrow (BM), 2) ≥ 30% blasts + promyelocytes in PB or BM (< 30% blasts alone), 3) ≥ 20% basophils in PB or BM, or 4) platelets < 100,000/mm^3 unrelated to drug therapy.
- Primary or acquired hematologic resistance to imatinib defined as any of the following: 1) Chronic phase CML that progressed to accelerated phase during treatment with imatinib ≥ 400 mg/day (primary or acquired resistance), 2) Accelerated phase CML unresponsive (4 weeks of treatment, or 2 if rapid progression) to imatinib ≥ 600 mg/day (primary resistance), or 3) progression to accelerated phase CML after initial response of accelerated or blast phase CML to imatinib ≥ 600 mg/day.
- Imatinib intolerance defined as either: 1) toxicity possibly related to imatinib ≤ 400 mg/day that led to discontinuation of imatinib, or 2) ability to tolerate only < 400 mg/day imatinib.
- ECOG PS 0 – 2.
- Adequate hepatic (serum bilirubin ≤ 2.0 x ULN), ALT or AST ≤ 2.5 x ULN) and renal functions (serum creatinine ≤ 1.5 x ULN).
- Normal serum K, Mg, Ca.

Key Exclusion Criteria:

- See list for CA180013.
- Received imatinib within 7 days, interferon or cytarabine within 14 days, a targeted small molecule anti-cancer agent within 14 days, any investigational agent within 28 days (hydroxyurea and anagrelide permitted).

Treatments Administered:

Dasatinib was administered at an oral dose of 70 mg BID (q12h).

- Dose escalation to 100 mg BID in patients 1) with rising blast percentages on 2 consecutive blood counts at least 1 week apart, or 2) with no CHR within 1 month, or 3) no CCyR after 3 months, or 4) loss of response.
- Treatment interruption as under CA180017.
- Dose reduction to 50 mg BID and a second reduction to 40 mg BID permitted.
- Drug discontinuation as under CA180017.

Concomitant treatment was as described under CA180013.

Study Assessments:

At study entry: history and physical examination, eligibility assessments, assessments of baseline signs and symptoms, including HRQoL, 12-lead ECG, Chest X-ray, CBC, PT/INR/PTT, serum chemistry, CD4 + T-cell count, urinalysis, CK, CK-MB, cardiac troponin I, troponin T, bone marrow aspirate/biopsy, FISH, mutation analysis sample, and quantitative PCR.

Weekly and at end of treatment: targeted physical examination, vital signs, CBC, differential, platelet count, PT/INR/PTT, serum chemistry, CD4 + T-cell count, and urinalysis. CK, CK-MB, cardiac troponin I, troponin T weekly during the 1st cycle only.

Bone marrow aspirate/biopsy: after each cycle and end of treatment.
ECGs: on Days 1 and 8 of the 1st cycle, and after each cycle. ECGs were read centrally.
PS: after each cycle.
Adverse event assessments: continuous.
Assessments of medications used: after each cycle.

Efficacy Assessments: Hematologic and Cytogenetic response criteria were listed under 6.0 Efficacy section.
Disease Progression was defined as any of the following:

- MaHR followed by failure to maintain MaHR over a consecutive 2-week period after starting the maximum dose of dasatinib.
- MiHR followed by failure to maintain MiHR over a consecutive 2-week period after starting the maximum dose of dasatinib.
- No decrease from % blasts in PB or BM on all assessments over a consecutive 4-week period after starting the maximum dose of dasatinib.
- Blast phase CML after MaHR or MiHR.
- Blast phase CML after no hematologic response.
- Investigator's report of disease progression or death.

Protocol Deviations: Thirteen (13) subjects were listed as having a possible protocol deviation, because < 100,000 platelets/mm^3 may have been due to hydroxyurea; 1 subject reached 30% blast count during enrollment, but previously had 15% - 30% blast counts; 1 subject had not initially met the criteria for accelerated CML, but later did; 1 subject had met the criteria, but these data were not entered into the database. *Reviewer's comment: there were no significant protocol deviations.*

Population Data Sets:

- Treated subjects: all subjects who received at least 1 dose of dasatinib (107).
- Evaluable subjects for cytogenetic response: all treated subjects who have at least 1 on study valid cytogenetic assessment (i.e. > 0 metaphases) or who discontinued prior to the first on study cytogenetic assessment (98).
- Evaluable subjects for cytogenetic response with at least 20 metaphases (85).
- Additionally enrolled subjects: all subjects who were enrolled after May 12, 2005 (77).

Disposition of Study Subjects

Of the 120 enrolled subjects, 107 (99 imatinib-resistant and 8 imatinib-intolerant) received at least one dose of dasatinib. Thirteen (13) enrolled subjects were not treated; 6 never received dasatinib and 7 were switched to a different protocol. Of the 107 treated subjects, 82 were still on treatment at the time of the 6-month on-study summary. Of the 25 subjects who withdrew from the study, the reasons for withdrawal are shown below in Reviewer's Table A34 (data from Sponsor's Table 4.1).

Reviewer's Table A34. CA180005. Subject Disposition – All Treated Subjects

Disposition	**Imatinib-intolerant N = 8**	**Imatinib-resistant N = 99**	**Total N = 107**
On Treatment	8 (100%)	74 (75%)	82 (77%)
Off Treatment		25 (25%)	25 (23%)
- Disease Progression	0	10 (10%)	10 (9%)
- Dasatinib Toxicity	0	4 (4%)	4 (4%)
- AE unrelated to dasatinib	0	1 (1%)	1 (1%)
- Subject request	0	3 (3%)	3 (3%)
- Death	0	4 (4%)	4 (4%)
- Other	0	3 (3%)	3 (3%)

Demographic and Baseline Characteristics

Demographic characteristics of the study population were representative of patients with accelerated phase CML (Reviewer's Table A35, data from Sponsor's Table 5.3). The ages of subjects ranged from 23 to 86 years; males and females were equally represented; most of the subjects were White (Caucasian); 47% had ECOG PS of 0, 39%, of 1, and 14%, of 2 (not allowed under inclusion criteria).

Reviewer's Table A35. CA180005. Demographic Characteristics – All Treated Subjects

Characteristic	Intolerant, N = 8	Resistant, N = 99
Age, years		
Mean ± SD	64.8 ± 6.9	55.0 ± 13.2
Median (min – max)	67.0 (54 – 74)	57 (23 – 86)
21-45 years	0	23 (23%)
46-65	3 (38%)	55 (56%)
66-75	5 (63%)	18 (18%)
> 75	0	3 (3%)
Gender		
Male	2 (25%)	53 (54%)
Female	6 (75%)	46 (46%)
Race		
White	8 (100%)	84 (85%)
Black/African American	0	5 (5%)
Asian	0	10 (10%)
ECOG PS		
0	3 (38%)	47 (48%)
1	4 (50%)	38 (38%)
2	1 (12%)	14 (14%)

Disease history is summarized in Reviewer's Table A36 below (data from Sponsor's Table 5.4.1A). Generally, subjects had long histories of CML; the median duration was 91 months for all treated subjects. All had been extensively treated with chemotherapy, interferon, bone marrow transplant, radiotherapy, and hydroxyurea or anagrelide. Most (68%) had more than 3 years of imatinib therapy, and 59% had been treated with high-dose imatinib (> 600 mg/day). Most had had good responses to imatinib, 83% CHR and 32% MCyR.

The reasons for imatinib intolerance in 8 subjects were pancytopenia, neutropenia, thrombocytopenia, arthralgia/myalgia, gastrointestinal symptoms, and rash.

Reviewer's Table A36. Baseline Disease and Previous CML Therapy Characteristics

Characteristic	Intolerant, N = 8	Resistant, N = 99
Time from initial diagnosis (months)		
Median (min – max)	68.7 (4.3 – 108.7)	91.2 (7.6 – 355.1)
Length of imatinib therapy, no. of subjects (%)		
< 1 year	4 (50%)	4 (4%)
1 – 3 years	2 (25%)	24 (24%)
> 3 years	2 (25%)	71 (72%)
Highest dose		
< 400 mg/day	0	0
400 -600 mg/day	5 (63%)	39 (39%)
> 600 mg/day	3 (38%)	60 (61%)

Best hematologic response to imatinib		
CHR	5 (63%)	84 (84%)
Return to chronic phase	1 (13%)	5 (5%)
Stable	0	7 (7%)
Progression	1 (13%)	2 (2%)
Unable to determine	1 (13%)	1 (1%)
Best cytogenetic response to imatinib		
CCyR	1 (13%)	10 (10%)
PCyR	0	23 (23%)
Other	6 (75%)	64 (65%)
Previous other therapy (no. of subjects, %)		
Bone marrow transplant	2 (25%)	17 (17%)
Radiotherapy	0	4 (4%)
Chemotherapy	4 (50%)	68 (69%)
Interferon	4 (50%)	76 (77%)
Hydroxyurea or anagrelide	7 (88%)	96 (97%)

Baseline Hematologic Status

Baseline hematologic parameters are shown in Reviewer's Table A37 below (data from Sponsor's Table 5.4.1.C). Nineteen patients had extra-medullary involvement, spleen in 18 subjects and liver in 5. Forty-two (42%) of subjects had WBC ≥ 20,000/mm³, 41% were thrombocytopenic (platelets < 100,000/mm³), 19% had basophilia of ≥ 20% basophils in PB, 67% had blasts in PB and 32% had ≥ 15% blasts in the bone marrow.

Reviewer's Table A37. CA180005. Baseline Hematologic Disease Status

Characteristic	**Imatinib-intolerant** **N = 8**	**Imatinib-resistant** **N = 99**
WBC median (min – max) < 20,000/mm³ ≥ 20,000/mm³	5,600/mm³ (3,200 – 68,400) 5 subjects (63%) 3 subjects (38%)	17,500/mm³ (1,000 – 243,400) 56 subjects (57%) 42 subjects (42%)
Basophils in PB No. of subjects (%) Median (min – max)	5 (63%) 11% (5% – 13%)	73 (74%) 8% (0% – 63%)
Platelet count, median (min – max)	165,500/mm³ (54,000 – 1,463,000)	164,500/mm³ (8,000 – 3,580,000)
Blasts in PB No. of subjects (%) Median % (min – max)	5 subjects (63%) 7% (0 - 21%)	67 subjects (68%) 2.0% (0 – 68%)
Blasts in BM No. of subjects Median % (min – max)	7 (88%) 15% (0 – 20%)	94 (95%) 8.9% (0 – 60%)
Involvement of spleen, liver, nodes, other organs	2 spleen	16 spleen, 5 outside spleen

Extent of Exposure

The Sponsor presents the extent of exposure data in two ways: by the duration of treatment and the dosing during that time, and by the total number of days that subjects received the study drug and the dosing during those days. The difference between the two sets are the dose interruption periods.

The median duration of treatment at the interim analysis time point (minimum 12 weeks' treatment) was 4.21 months, but the duration of treatment when subjects received dasatinib was 3.48 months. Treatment was interrupted during 0.73 months, or during 17% of the treatment period. The average daily dose when actually taken was very close to the dose planned, median of 137 mg/day, and 61% of subjects received > 90% of the planned dose. Taking into account the dose interruptions, the average daily dose was 119 mg/day.

Reviewer's Table A38. CA180005. Dose Intensity and Duration of Treatment – All Treated Subjects

	Imatinib-intolerant N = 8	**Imatinib-resistant N = 99**	**Total N = 107**
Daily dose, median (min – max)	78.0 (66.0 – 114.0)	126.0 (60.0 – 189.0)	119.0
Percentage of dose administered			
< 90%	8 patients (100%)	50 (51%)	58 (54%)
> 90 -100%	0	39 (39%)	39 (36%)
> 100%	0	10 (10%)	10 (9%)
Duration of treatment			
Median no. months (min – max)	4.96 (4.24 – 7.36)	3.81 (0.20 – 8.28)	4.21
Patients treated for			
≤ 3 months	0	22 patients (21%)	22 (21%)
3 – 6 months	6 (75%)	66 (67%)	72 (67%)
> 6 months	2 (25%)	11 (11%)	13 (12%)

Reviewer's Table A39. CA180005. Dose Intensity and Extent of Exposure – All Treated Subjects

	Imatinib-intolerant N = 8	**Imatinib-resistant N = 99**	**Total N = 107**
Daily dose, median (min – max)	116.0 (102.0 – 139.0)	138.0 (94.0 – 189.0)	137.0
Percentage of dose administered			
< 90%	6 patients (75%)	35 (35%)	41 (38%)
> 90 -100%	2 (25%)	54 (55%)	56 (52%)
> 100%	0	10 (10%)	10 (9%)
Duration of treatment			
Median no. months (min – max)	3.91 (2.56 – 5.29)	3.45 (0.20 – 8.28)	3.48
Patients treated for			
≤ 3 months	1 (13%)	36 patients (36%)	37 (35%)
3 – 6 months	7 (87%)	55 (56%)	62 (58%)
> 6 months	0	8 (8%)	8 (8%)

Discontinuation of Study Therapy

A total of 20 subjects (19%) discontinued study treatment, all in the imatinib-resistant group. The reasons for discontinuations were as follows:

- Disease progression (9)
- Dasatinib toxicity (2)
- AE unrelated to study drug (1)
- Subject request (3)
- Death (4), and
- Other (lack of CyR) (1).

Dose Reductions, Interruptions and Escalations

Dose reductions occurred in 52 (49%) subjects because of hematologic toxicity (in 28) and non-hematologic toxicity (in 13). Non-hematologic toxicities were GI bleeds (in 4), diarrhea (in 2), headache (in 2), asthenia, renal insufficiency, arrhythmia, and pneumonia (1 in each).

Dose interruptions occurred in 71 (66%) subjects because of hematologic (in 35) and non-hematologic (in 31) toxicities. The latter were GI bleed (in 4), diarrhea (in 3), fever (in 3), and a great variety of toxicities in 1 or 2 subjects. Of note, 2 subjects had pleural effusion, 2 had QT prolongation, and 1 had rhabdomyolysis. Dose interruption was followed by dose reductions in 43 of the 71 subjects. The median time to first dose reduction/interruption was 37 days. The median duration of first interruption was 13 days.

The dose was increased to 100 mg BID in 13 subjects. The reasons were no CHR within 1 month, rising blasts, loss of response, and rising WBC.

Efficacy Results

Primary Efficacy Endpoints: Primary efficacy endpoint hematologic response rates (MaHR and OHR) are shown in Reviewer's Table A40 (data from Sponsor's Table 4.2).

The MaHR rate after a median follow up of 6 months was 59% and the OHR rate was 80%. Response rates were about the same in the imatinib-resistant and in the small number of imatinib-intolerant subjects.

Reviewer's Table A40. CA180005. Primary Efficacy Endpoints Confirmed OHR and MaHR – All Treated Subjects

Response Type	Imatinib-intolerant N = 8	Imatinib-resistant N = 99	Total N = 107
Confirmed MaHR (CHR + NEL)	5 (63%)	58 (59%)	63 (59%)
Confirmed OHR (CHR + MiHR + NEL)	6 (75%)	80 (81%)	86 (80%)

Secondary Efficacy Endpoints: Confirmed CHR, MiHR, and NEL, Major cytogenetic response (MCyR), Durability of OHR and MaHR, and Time to OHR and MaHR.

CHR occurred in 33% of patients. NEL response was found in 26%, and MiHR, in 22%. Twenty percent (20%) of subjects had no response. These data are shown in Reviewer's Table A41 (from Sponsor's Tables 4.2 and 4.3A).

In the all treated population, MCyR occurred in 31% of subjects, 32% (23% CCyR and 9% PCyR) in imatinib-resistant subjects and 13% (in the imatinib-intolerant subjects). The results were similar in the evaluable subject population; MCyR occurred in 32% of subjects. In the population with CyR based on ≥ 20 metaphases, the MCyR rate was 33% (in 26 of 80 subjects).

Reviewer's Table A41. Secondary Efficacy Endpoints MCyR, Confirmed CHR and NEL – All Treated Subjects

Best Hematologic & Cytogenetic Response	Imatinib-intolerant N = 8	Imatinib-resistant N = 99	Total N = 107
MCyR	1 (13%)	32 (32%)	33 (31%)
---CCyR	0	23 (24%)	23 (22%)
---PCyR	1 (14%)	9 (9%)	10 (10%)
Confirmed CHR	2 (25%)	33 (33%)	35 (33%)
Confirmed NEL	3 (38%)	25 (25%)	28 (26%)
Confirmed MiHR	1 (13%)	22 (22%)	23 (22%)
No response	2 (25%)	19 (19%)	21 (20%)

Hematologic and cytogenetic responses mainly occurred during the first 3 months of dasatinib therapy. The MCyR rate increased from 28% at 3-months to 31% at 6 months, the MaHR from to 55% to 59%, and the OHR from 79% to 80%.

The median time to achieve a MaHR was 57 days. Among the 63 patients who had achieved a MaHR, only one progressed during the period of follow-up. The longest duration of MaHR had been > 9.5 months (Figure 3 in Efficacy).

Among the 86 subjects who had an OHR, 6 subjects (all imatinib-resistant) progressed. The median time to OHR was 30 days.

10.1.5 Myeloid Blast Phase CML. CA18006: A Phase 2 Study of Dasatinib (BMS-354825) in Subjects with Myeloid Blast Phase CML Resistant to or Intolerant of Imatinib Mesylate.

Study Status: The study was started on December 30, 2004 and is ongoing. Accrual was closed on July 1, 2005 with 124 subjects enrolled. The submission contains data on the first 80 subjects enrolled on or before May 17, 2005, treated on or before May 18, 2005. Of the first 80 enrolled subjects, 74 were treated. Of these, 68 were imatinib-resistant and 6 were imatinib-intolerant. The minimum 3-months follow-up data cutoff date was October 17, 2005 and the minimum 6-month follow-up data cutoff date of November 11, 2005.

Study Objectives:
Primary: To estimate the MaHR and OHR rates to dasatinib in myeloid blast phase CML subjects with primary or acquired resistance to imatinib.

Secondary:
- To assess the durability of hematologic response and time to hematologic response (OHR and MaHR) in the imatinib-resistant group and imatinib-intolerant groups separately.
- To assess cytogenetic and molecular responses in the imatinib-resistant group.
- To assess hematologic, cytogenetic, and molecular responses in the imatinib-intolerant group.
- To measure HRQoL using the Functional Assessment of Cancer Therapy-General questionnaire.
- To assess further the safety and tolerability of dasatinib.

Study Design: Open-label, multicenter Phase 2 study of dasatinib in subjects with imatinib-resistant myeloid blast phase CML. A separate group of imatinib-intolerant subjects was also enrolled. Dasatinib dose was 70 mg BID. Dose modifications for disease progression (dose increase to 100 mg BID) or toxicity (dose reduced up to 2 times, to 50 mg BID, then to 40 mg BID) were specified. Treatment continued until disease progression or development of intolerable toxicity. All subjects were followed for a minimum of 30 days after the last dose of dasatinib or until recovery from toxicity.

Study Population:
Key Inclusion Criteria:
- Men and women, at least 18 years of age, who signed an informed consent.

- Ph+ (or BCR-ABL) myeloid blast phase CML defined as manifesting at least one of the following: 1) ≥ 30% blasts in peripheral blood (PB) or bone marrow (BM), 2) extramedullary infiltrates of leukemic cells (other than in spleen or liver) with PB myeloid blast morphology.
- Hematologic resistance to imatinib defined as any of the following: 1) Chronic phase CML that progressed to myeloid blast phase during treatment with imatinib ≥ 400 mg/day (primary resistance in case of subjects who had no response to imatinib or acquired resistance in subjects who responded and subsequently progressed to myeloid blast phase), 2) Accelerated phase CML who progressed to myeloid blast phase CML while on treatment with imatinib dose of ≥ 600 mg/day (or 400 – < 600 mg/day if the subject is intolerant of ≤ 600 mg/day, or 3) subjects diagnosed with myeloid blast phase CML who meet the criteria for myeloid blast crisis after at least 4 weeks of treatment with imatinib ≥ 600 mg/day. This 4-week treatment requirement can be shortened to 2 weeks for rapidly progressing patients.
- Imatinib intolerance defined as either: 1) toxicity possibly related to imatinib ≤ 400 mg/day that led to discontinuation of imatinib, or 2) ability to tolerate only < 400 mg/day imatinib.
- ECOG PS 0 – 2.
- Adequate hepatic (serum bilirubin ≤ 2.0 x ULN), ALT or AST ≤ 2.5 x ULN) and renal functions (serum creatinine ≤ 1.5 x ULN).
- Normal serum K, Mg, Ca.

Key Exclusion Criteria:

- See lists for CA180017 and CA180013.

Treatments Administered:

Dasatinib was administered at an oral dose of 70 mg BID (approximately q.12 hours).

- Dose escalation to 100 mg BID in patients 1) with rising blast percentages on 2 consecutive blood counts at least 1 week apart, or 2) with no CHR within 1 month of dasatinib therapy, or 3) no CCyR after 3 months of dasatinib therapy, or 4) loss of response.
- Treatment interruption as under CA180017.
- Dose reduction to 50 mg BID and a second reduction to 40 mg BID permitted.
- Drug discontinuation as under CA180017.

Concomitant treatment as under CA180017.

Study Assessments:

At study entry: history and physical examination, eligibility assessments, assessments of baseline signs and symptoms, including HRQoL, 12-lead ECG, Chest X-ray, CBC, PT/INR/PTT, serum chemistry, CD4 + T-cell count, urinalysis, CK, CK-MB, cardiac troponin I, troponin T, bone marrow aspirate/biopsy, FISH, mutation analysis sample, and quantitative PCR.

Cycles 1 and 2. Weekly and at end of treatment: targeted physical examination, vital signs, CBC, differential, platelet count, PT/INR/PTT, serum chemistry, CD4 + T-cell count, and urinalysis. CK, CK-MB, cardiac troponin I, troponin T weekly during the 1st cycle only.

Cycle 3 and subsequent cycles. Weekly: CBC, differential, platelet count. Every 2 weeks: targeted physical examination, vital signs, PS, HRQoL, PT/INR/PTT, serum chemistry. Every 4 weeks: CD4 + T-cell count.

Bone marrow aspirate/biopsy, FISH, RT-PCR: every 12 weeks and the end of treatment.
ECGs: on Days 1 and 8 of the 1st cycle, and after each cycle. ECGs were read centrally.
PS: after each cycle.
Adverse event assessments: continuous.
Assessments of medications used: after each cycle.

Efficacy Assessments: Definitions of hematologic responses (MaHR, CHR, NEL, and MiHR) are shown under Efficacy Endpoints (6.1.2). Confirmed responses must have been confirmed at least 4 weeks after first documented. A subject will have a MaHR if they meet the criteria for either CHR or NEL. Subjects with MaHR have MiHR. The OHR is defined as the proportion of subjects with MaHR or MiHR. Cytogenetic responses (MCyR, CCyR and PCyR) are defined above in 6.1.2. Disease progression is defined above in 6.1.2.

Population Data Sets:

- Treated subjects: all subjects who received at least 1 dose of dasatinib (74 subjects).
- Evaluable subjects for cytogenetic response: all treated subjects who have at least 1 on study valid cytogenetic assessment (i.e. > 0 metaphases) or who discontinued prior to the first on study cytogenetic assessment (71 subjects).
- Evaluable subjects for cytogenetic response with at least 20 metaphases (62 subjects).
- Additionally enrolled subjects: all subjects who were enrolled after the first 80 subjects up to May 17, 2005 (44 subjects).

Protocol Deviations: One subject was listed as not meeting the criteria for myeloid blast phase CML. The diagnosis was based on PB blasts of 33%, which occurred prior to the 13% blasts listed in the CRF. *Reviewer's comment: there were no significant protocol deviations.*

Disposition of Study Subjects

Of the 80 enrolled subjects, 74 (68 imatinib-resistant and 6 imatinib-intolerant) received at least one dose of dasatinib (Treated population). Six subjects were not treated. Three did not meet the criteria for myeloid blast phase CML, two died, one was a screening failure (had a prolonged QT interval). At the time of the minimum 6-month on-study summary, 32 (43%) were still on treatment. The reasons for discontinuing dasatinib therapy are shown in Reviewer's Table A42 below (data from Sponsor's Table 5.1). The most common reason for discontinuation from the study was disease progression (22 subjects). Seven subjects had died. Five discontinued because of drug toxicity. The median duration of treatment among the subjects still on study was 29 weeks (range 24 – 41 weeks).

Reviewer's Table A42. CA180006. Subject Disposition - Treated Subjects

Disposition	Imatinib-intolerant N = 6	Imatinib-resistant N = 68	Total N = 74
On Treatment	3 (50%)	29 (43%)	32 (43%)
Off Treatment	3 (50%)	39 (57%)	42 (57%)
- Disease Progression	1 (17%)	21 (31%)	22 (30%)
- Dasatinib Toxicity	0	5 (7%)	5 (7%)
- AE unrelated to dasatinib	0	2 (3%)	2 (3%)
- Death	1 (17%)	6 (9%)	7 (10%)
- Non-compliance	0	1 (2%)	1 (1%)
- Other	1 (17%)	4 (6%)	5 (7%)

Demographic and Baseline Characteristics

Demographic characteristics of the study population were representative of patients with myeloid blastic phase CML (Reviewer's Table A43, data from Sponsor's Table 5.3). About 30% of subjects were between 21 and 45 years of age; about 49%, between 46 and 65; and about 22%, between 66 and 75. Thus, the majority of subjects (78%) were younger than 66 years. Males and females were about equally represented. Most of the subjects (76%) were White (Caucasian). About 58% of the subjects had ECOG PS of 0 or 1; 38% had PS 2.

Reviewer's Table A43. CA180006. Demographic characteristics – All Treated Subjects

Characteristic	Intolerant, N = 6	Resistant, N = 68	Total, N = 74
Age, years			
Mean ± SD	58.0 ± 9.9	51.8 ± 13.4	52.3
Median (min – max)	60.5 (54 – 74)	54.5 (21 – 71)	55.0 (21 – 71)
21-45 years	1 (17%)	21 (31%)	22 (30%)
46-65	4 (67%)	32 (47%)	36 (49%)
66-75	1 (17%)	15 (22%)	16 (22%)
Gender			
Male	2 (33%)	39 (57%)	41 (55%)
Female	4 (67%)	29 (43%)	33 (45%)
Race			
White	6 (100%)	50 (74%)	56 (76%)
Black/African American	0	7 (10%)	7 (10%)
Asian	0	11 (16%)	11 (15%)
ECOG PS			
0	1 (17%)	12 (18%)	13 (18%)
1	3 (50%)	27 (40%)	30 (41%)
2	2 (33%)	26 (39%)	28 (38%)
3	0	1 (2%)	1 (1%)
Not reported	0	2 (3%)	2 (3%)

Disease history is summarized in Reviewer's Table A44 below (data from Sponsor's Tables 5.4.1A and B). Generally, subjects had long histories of CML. The median time from initial CML diagnosis to first dose of dasatinib was about 49 months for all treated subjects. The median time from CML diagnosis was shorter in imatinib-resistant subjects (47 months) than in imatinib-intolerant subjects (72.5 months). All had been extensively treated with chemotherapy, interferon, bone marrow transplant, radiotherapy, and hydroxyurea or anagrelide. About one-half of the subjects (47%) had more than 3 years of imatinib therapy, and 49% had been treated with high-dose imatinib (> 600 mg/day). Most had had good responses to imatinib, 84% CHR and 46% MCyR.

The reasons for imatinib intolerance in 6 subjects were neutropenia, leukopenia, hepatotoxicity, toxic hepatitis, gastrointestinal symptoms, and rash.

Reviewer's Table A44. CA180006. Baseline Disease and Previous CML Therapy

Characteristic	**Intolerant N = 6**	**Resistant N = 68**	**Total N = 74**
Time from initial diagnosis (months) Median (min – max)	72.5 (39.0 – 129.5)	47.0 (3.3 – 215.5)	48.9 (3.3 – 215.5)
Length of imatinib therapy, no. of subjects (%)			
< 1 year	1 (17%)	10 (15%)	11 (15%)
1 – 3 years	1 (17%)	27 (40%)	28 (38%)
> 3 years	4 (67%)	31 (46%)	35 (47%)
Highest dose			
< 400 mg/day	0	0	0
400 -600 mg/day	6 (100%)	32 (47%)	38 (51%)
> 600 mg/day	0	36 (53%)	36 (49%)
Best hematologic response to imatinib			
CHR	6 (100%)	56 (82%)	62 (84%)
Return to chronic phase	0	3 (4%)	3 (4%)
No evidence of leukemia (NEL)	0	1 (2%)	1 (2%)
Stable	0	3 (4%)	3 (4%)
Progression	0	2 (3%)	2 (3%)
Unable to determine	0	3 (4%)	3 (4%)
Best cytogenetic response to imatinib			
CCyR	2 (33%)	22 (32%)	24 (32%)
PCyR	1 (17%)	9 (13%)	10 (14%)
Other	3 (50%)	36 (53%)	39 (53%)
Not reported	0	1 (2%)	1 (1%)
Previous other therapy (no. of subjects, %)			

Bone marrow transplant	1 (17%)	8 (12%)	9 (12%
Radiotherapy	1 (17%)	8 (12%)	9 (12%)
Chemotherapy	2 (33%)	47 (69%)	49 (66%)
Interferon	6 (100%)	35 (52%)	41 (55%)
Hydroxyurea or anagrelide	6 (100%)	59 (87%)	65 (88%)

Baseline Hematologic Status

Baseline hematologic parameters are shown in Reviewer's Table A45 below (data from Sponsor's Table 5.4.1.C). Thirteen patients (18%) had involvement of the spleen and 14 patients had involvement outside spleen. Thirty-four (46%) of subjects had WBC ≥ 20,000/mm³, 53 (72%) were thrombocytopenic (platelets < 100,000/mm³), 50 (68%) had blasts in PB and 26 (35%) had ≥ 50% blasts in the bone marrow.

Reviewer's Table A45. Baseline Hematologic Disease Status

Characteristic	**Imatinib-intolerant N = 6**	**Imatinib-resistant N = 68**	**Total N = 74**
WBC median (min – max) < 20,000/mm³ ≥ 20,000/mm³	5,000/mm³ (1,000 – 24,800) 5 subjects (83%) 1 subjects (17%)	18,200/mm³ (400 – 191,600) 35 subjects (52%) 33 subjects (49%)	16,600/mm³ (400 – 191,600) 40 (54%) 34 (46%)
Platelet count, median (min – max) < 100,000/mm³ ≥ 100,000/mm³	60,500/mm³ (18,000 – 1,191,000) 4 subjects (67%) 2 subjects (33%)	51,000/mm³ (10,000 – 2,121,000) 49 subjects (72%) 19 subjects (28%)	51,000/mm³ (10,000 – 2,121,000) 53 subjects (72%) 21 subjects (28%)
Blasts in PB No. of subjects (%) Median % (min – max)	3 subjects (50%) 3% (3 - 16%)	47 subjects (69%) 40.0% (0 – 100%)	50 subjects (68%) 39.0% (0 – 100%)
Blasts in BM No. of subjects Median % (min – max)	5 (83%) 50% (12 – 67%)	62 (91%) 40% (0 – 95%)	67 (91%) 40% 0 – 95%)
Involvement of spleen, liver, nodes, other organs	2 spleen 1 outside spleen	11 spleen 13 outside spleen	13 (18%) 14 (19%)

Extent of Exposure

The Sponsor presents the extent of exposure data in two ways: by the duration of treatment and the dosing during that time, and by the total number of days that subjects received the study drug and the dosing during those days. The difference between the two sets is due to dose interruption periods. These data are shown in Reviewer's Tables A46 and A47 (data from Sponsor's Tables 6.1A and 6.1B).

The median duration of treatment at the interim analysis time point (minimum 12 weeks' treatment) was 3.29 months, but the duration of treatment when subjects received dasatinib was 3.48 months. Treatment was interrupted during 0.73 months, or during 17% of the treatment period. The average daily dose when actually taken was very close to the dose planned, median of 137 mg/day, and 61% of subjects received > 90% of the planned dose. Taking into account the dose interruptions, the average daily dose was 119 mg/day.

Reviewer's Table A46. CA180006. Dose Intensity and Duration of Treatment – All Treated Subjects

	Imatinib-intolerant N = 6	**Imatinib-resistant N = 68**	**Total N = 74**
Average daily dose, median (min – max)	134.5 (82.0 – 140.0)	136.5 (58.0 – 190.0)	136.5
Percentage of dose administered			
< 90%	2 patients (33%)	25 (37%)	27 (37%)
> 90 -100%	4 (67%)	27 (40%)	31 (42%)
> 100%	0	16 (24%)	16 (22%)
Duration of treatment			
Median no. months (min – max)	3.99 (1.74 – 7.00)	3.21 (0.03 – 7.36)	3.29
Patients treated for			
≤ 3 months	2 (33%)	30 (44%)	32 (43%)
3 – 6 months	2 (33%)	34 (50%)	36 (49%)
> 6 months	2 (33%)	4 (6%)	6 (8%)

Reviewer's Table A47. CA180006. Dose Intensity and Extent of Exposure – All Treated Subjects

	Imatinib-intolerant N = 6	**Imatinib-resistant N = 68**	**Total N = 74**
Daily dose, median (min – max)	138.5 (123.0 – 141.0)	140.0 (70.0 – 190.0)	140.0
Percentage of dose administered			
< 90%	1 patient (17%)	13 (19%)	14 (19%)
> 90 -100%	4 (67%)	33 (49%)	37 (50%)
> 100%	0	22 (32%)	23 (31%)
Duration of treatment			
Median no. months (min – max)	3.88 (1.74 – 7.00)	2.83 (0.03 – 7.36)	2.91
Patients treated for			
≤ 3 months	2 (33%)	37 patients (54%)	39 (53%)
3 – 6 months	2 (33%)	27 (40%)	30 (41%)
> 6 months	2 (33%)	4 (6%)	5 (7%)

Dose Reductions, Interruptions and Escalations (Minimum 3-month Follow-up Data)

Dose reductions occurred in 26 (35%) subjects, because of hematologic toxicities in 13 (18%) and non-hematologic toxicities in 9 (12%). Non-hematologic toxicities were GI bleeding, rash, diarrhea-abdominal pain-anorexia, hepatic and renal toxicity, tumor lysis syndrome, cardiac ischemia, Sweet's syndrome, prolonged QTc, and return to chronic phase (1 case of each).

Dose interruptions occurred in 43 (58%) subjects, because of hematologic toxicities in 17 (23%) and non-hematologic toxicities in 22 (30%). The latter were GI bleeding, rising troponin T level, diarrhea, pneumonia, and rash in 2 subjects each, and tarry stool, pulmonary infiltrates, hematuria, cholecystitis, hepatic and renal toxicity, arrhythmia, congestive heart failure, and pleural effusion in 1 subject each. First dose reduction/interruption due to toxicity occurred in 42 (57%) subjects. The median time to first dose reduction/interruption was 32 days. The median duration of first interruption was 12.5 days.

The dose was increased in 30 subjects (41%). The increase was to 100 mg BID in 28 subjects (38%). The reasons were "rising % blasts" in 15 subjects, no CHR within 1 month in 8, loss of response in 3, and other reasons in 4, including an investigator's decision upon finding the T315 mutation in one subject.

Efficacy Results

Primary Efficacy Endpoints: Major Hematologic Response (MaHR) and Overall Hematologic Response (OHR).

Primary efficacy endpoint hematologic response rates are shown in Reviewer's Table A48 (data from Sponsor's Table 4.2). The MaHR rate after a median follow up of 6 months was 32% and the OHR rate was 53%. The longest duration of MaHR had been > 7.8 months and the shortest duration was > 1.2 months. The median time to achieve MaHR was 57 days. The longest duration of OHR was > 9 months, and the shortest was > 2.2 months. The median time to OHR was 30 days.

At the minimum 6-month follow-up time, 35 subjects had progressed. None of the subjects with MaHR had progressed. Among the 39 subjects who achieved any hematologic response (OHR), 5 subjects (all imatinib-resistant) had progressed. Disease progression in these 5 subjects occurred after a median time of 2.3 months (range, 1.2 – 4.3 months). The remaining 30 subjects who progressed did not have a hematologic response.

Reviewer's Table A48. CA180006. Primary Efficacy Endpoints Confirmed OHR and MaHR – All Treated Subjects

Response Type	Imatinib-intolerant N = 6	Imatinib-resistant N = 68	Total N = 74
Confirmed MaHR (CHR + NEL)	1 (17%)	23 (34%)	24 (32%)
Confirmed OHR (CHR + MiHR + NEL)	3 (50%)	36 (53%)	39 (53%)

Secondary Efficacy Endpoints: Confirmed CHR, MiHR, and NEL, Major cytogenetic response (MCyR), Durability of OHR and MaHR, and Time to OHR and MaHR.

CHR occurred in 33% of subjects, NEL response was found in 26%, and MiHR in 22%. In 20% of subjects there was no response. These data are shown in Reviewer's Table A49 (from Sponsor's Tables 4.2 and 4.3A).

In the all treated population, MCyR occurred in 30% of all subjects, 29% (27% CCyR and 3% PCyR) in imatinib-resistant subjects and 33% (in the imatinib-intolerant subjects). The results were similar in the evaluable subject population; MCyR occurred in 30% (22/73) of subjects. In the population with CyR based on ≥ 20 metaphases, the MCyR rate was 22% (in 16 of 74 subjects). *Reviewer's Note: Since response could not be determined in 31/74 subjects, the denominator should be 43 subjects. Therefore, in the population in which CyR was based on ≥ 20 metaphases, the MCyR was 37% (achieved in 16 of 43 subjects).*

Reviewer's Table A49. CA180006. Secondary Efficacy Endpoints MCyR, and Confirmed CHR and NEL – All Treated Subjects

Best Hematologic & Cytogenetic Response	Imatinib-intolerant N = 6	Imatinib-resistant N = 68	Total N = 74
MCyR	2 (33%)	20 (29%)	22 (30%)
---CCyR	2 (33%)	18 (27%)	20 (27%)
---PCyR	0	2 (3%)	2 (3%)
Confirmed CHR	1 (17%)	17 (25%)	18 (24%)
Confirmed NEL	0	6 (9%)	6 (8%)
Confirmed MiHR	2 (33%)	13 (19%)	15 (20%)
No response	3 (50%)	32 (47%)	35 (47%)

Hematologic and cytogenetic responses mainly occurred during the first 3 months of dasatinib therapy. The MCyR rate increased from 28% at 3 months to 30% at 6 months, the MaHR from to 30% to 32%, and the OHR from 51% to 53%.

Duration of MaHR is shown in Figure A6. All responders remained in response during the period of follow-up.

10.1.6 Ph+ALL/Lymphoid Blast Phase, CA180015: A Phase 2 Study of BMS-354825 in Subjects with Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Resistant to or Intolerant of Imatinib Mesylate

Study Status: The study was initiated on January 5, 2005 and is ongoing. This interim report includes data on the first 81 subjects enrolled at 34 sites on or before May 23, 2005 and treated on or before June 1, 2005, with a minimum of 6 months (24 weeks) follow-up for subjects who remained on study as of the data cutoff on October 20, 2005. 78 patients were treated and are included in the efficacy analysis.

Changes in the conduct of the study:

March 14, 2005 Amendment 01
Country Specific: Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, The Netherlands, Norway, Poland, Sweden, United Kingdom.

The changes incorporated in this amendment were:
1) removing the possibility of using anagrelide in case of thrombocytosis in patients with CML as this is not an approved indication for the use of anagrelide in Europe.
2) using only a bone marrow aspirate and not a systematic bone marrow biopsy in case of Grade 4 neutropenia, unless this is medically justified
3) clarifying eligibility criteria for Ph + ALL subjects (Subjects with pH+ ALL who experience progression or lack of response after both standard induction or consolidation chemotherapy plus imatinib at a dose of $\geq$ 600 mg/day (or 400 mg/day to < 600 mg/day if the subject is intolerant of 600 mg/day) after 4 weeks.

March 14, 2005 Amendment 02
Country Specific: Korea
As requested by the local regulatory agency, to remove reference to commercial availability as one of the reasons for study termination.

August 26, 2005 Amendment 03
All sites
Major changes included:
1) Modification of the hematologic response criteria. The changes to the hematologic response criteria for advanced subjects introduced the concept of a "major hematologic response" which groups complete hematologic response (CHR) and no evidence of leukemia (NEL) under one general category. This change was introduced to highlight the observation that subjects achieving NEL have a durability of response similar to CHR but may have some degree of neutropenia or thrombocytopenia due to a long history of previous treatments for CML or ALL and thus do not meet the full criteria of CHR. The definition of return to chronic phase (RTC) was renamed "minor hematologic response" to separate this category from CHR and NEL as the duration of response is expected to be shorter for this cohort.

2) Adjustment of the frequency of visits for month 3 and beyond for subjects that are both stable and responding to BMS-354825 (Dasatinib) treatment.

Study Objectives:
Primary Objective: The primary objective of this study is to estimate the major and overall hematologic response rates to dasatinib in lymphoid blast phase CML subjects and Ph+ ALL subjects with primary or acquired resistance to imatinib mesylate.

Secondary Objectives:
- To assess the durability of hematologic response and time to hematologic response (major and overall) in the imatinib resistant group.
- To assess cytogenetic and molecular responses in the imatinib resistant group.
- To measure the minor hematologic response rate in the imatinib resistant group.
- To assess hematologic, cytogenetic and molecular responses in the imatinib intolerant group. Further, durability and time to hematologic response will be assessed.
- To explore the role of BCR-ABL mRNA expression and point mutations in the BCR-ABL gene as predictors or surrogates of response.
- To measure health-related quality of life (HRQOL) using the FACT-G.
- To assess further the safety and tolerability of BMS-354825.
- Population PK will be performed on samples from the initial 60 treated subjects.

Study Design: This is an open-label Phase II study of dasatinib in subjects with a history of imatinib resistant or imatinib intolerant lymphoid blast phase CML or Ph+ ALL. The starting dose of dasatinib was 70 mg bid. Treatment continued until progression of disease despite escalation of the dose to 100 mg bid, until intolerable toxicity, or until withdrawal from study. Up to 2 dose reductions for toxicity were allowed (to 50 mg bid, then 40 mg bid). All subjects were to be followed for a minimum of 30 days after the last dose of study therapy or until recovery from all toxic effects, whichever is longer, and then at least every 4 weeks until all study-related toxicities resolved to baseline or ≤ CTC Grade 1, stabilized, or were deemed irreversible.

Eligibility Criteria:

Inclusion Criteria:
- Age ≥ 18 years
- Signed informed consent
- Subjects with Ph+ (or BCR/ABL+) lymphoid blast phase chronic myeloid leukemia whose disease has primary or acquired hematologic resistance* to imatinib mesylate or who are intolerant of imatinib mesylate**.
    - Subjects are considered to have lymphoid blast phase CML if there are at least 30% lymphoid blasts in peripheral blood or bone marrow and/or there are extramedullary infiltrates of leukemic cells (other than in spleen or liver) with peripheral blood lymphoid blast morphology.
- Subjects with Ph + ALL previously treated with standard induction or consolidation chemotherapy *and* progression or lack of response to imatinib at a dose of ≥ 600 mg/day (or 400 mg/day to < 600 mg/day if the subject is intolerant of 600 mg/day) after 4 weeks.

(A subject who tolerates a dose of imatinib 400 mg/day, but is intolerant of higher doses is not considered imatinib-intolerant.)

- ECOG performance status of 0-2
- Adequate hepatic function (bilirubin ≤2 x the institutional upper limit of normal (uln), AST and ALT ≤2.5 x the institutional uln
- Adequate renal function (serum creatinine ≤1.5 x uln)
- Normal potassium, magnesium and calcium (may be supplemented to achieve normal value)

Exclusion criteria:

- Women who are pregnant or breast-feeding, or (if of child-bearing potential) who are unwilling or unable to use appropriate contraception; and male patients whose partners of child-bearing potential are unwilling or unable to use appropriate contraception
- Subjects who are eligible and willing to undergo transplantation during the screening period
- Serious uncontrolled medical disorder or active infection
- Uncontrolled or significant cardiovascular disease including myocardial infarction within 6 months, angina or congestive heart failure within 3 months, diagnosed or suspected congenital long QT syndrome, or if QTc > 450 msec, history of significant ventricular arrhythmia, second or third degree heart block, bradycardia, uncontrolled hypertension
- Altered mental status which would prohibit the understanding or rendering of informed consent
- History of significant bleeding disorder unrelated to CML
- Other incurable malignancy
- Disorder that would prevent administration of study therapy
- Use of imatinib within 7 days, interferon or cytarabine within 14 days, other targeted small molecule anti-cancer agent within 14 days, and any other investigational or antineoplastic agent except hydroxyurea or anagrelide within 28 days
- Use of drugs with known risk of torsades de pointes (washout period required), irreversible platelet inhibitors or anti-coagulants (exceptions for anagrelide for thrombocytosis and low-dose warfarin)

*Hematologic resistance to imatinib was defined as

- Subjects initially diagnosed with chronic phase CML who progressed to lymphoid phase CML while on treatment with a prescribed imatinib dose of ≥ 400 mg/day. This includes subjects who had no response to imatinib (primary resistance) and those who responded and subsequently progressed to lymphoid blast phase (acquired resistance).
- Subjects initially diagnosed with accelerated phase CML who progressed to lymphoid phase CML while on treatment with a prescribed imatinib dose of ≥ 600 mg/day (or 400 mg to < 600 mg/day if the subject is intolerant of ≥ 600 mg/day). This includes subjects who had no response to imatinib (primary resistance) and those who responded and subsequently progressed to lymphoid blast phase (acquired resistance).
- Subjects initially diagnosed with lymphoid blast phase CML who meet the criteria for lymphoid blast phase after at least 4 weeks of treatment prescribed at a dose of ≥ 600

mg/day (or < 600 mg/day if the subject is intolerant of ≥ 600 mg/day). This 4 week treatment requirement can be shortened to 2 weeks for patients who are rapidly progressing. This includes subjects who had no response to imatinib (primary resistance) and those who responded and subsequently progressed back to lymphoid blast phase (acquired resistance).

**Imatinib intolerance
For purposes of defining intolerant subjects for this protocol a subject in lymphoid blast phase CML or with Ph+ ALL is defined as being intolerant of imatinib if he or she had a toxicity considered at least possibly related to imatinib at a dose of 400 mg/ day or lower which led to a discontinuation of therapy.
Note: Subjects must have had prior exposure to imatinib as defined above. However, imatinib mesylate does not need to be their most recent CML treatment prior to coming on this study.

Efficacy Assessments:
Complete blood count with platelets and white blood cell differential: weekly
Bone marrow aspirate and/or biopsy: screening, monthly during cycles 1-3, then every 12 weeks and end of treatment (includes cytogenetics; optional FISH)
Quantitative PCR for bcr-abl (performed on peripheral blood): screening and every 12 weeks for patients achieving a complete cytogenetic response

Efficacy Endpoints:
The co-primary endpoints were the major hematologic response rate and the overall (major plus minor) hematologic response rate in the imatinib resistant group. Criteria used to determine major hematologic response and CHR are described below.

A) Major Hematologic Response Criteria.
A subject will be determined to have a Major Hematologic Response if he/she meets the criteria for CHR or NEL:

1) Complete Hematologic Response (CHR)
A subject will be determined to have a CHR if he/she meets all of the following criteria:

- WBC ≤ Institutional upper limit of normal
- ANC ≥ 1000/mm3
- Platelets ≥ 100,000 /mm3
- No blasts or promyelocytes in peripheral blood
- Bone marrow blasts ≤ 5%
- < 5% myelocytes plus metamyelocytes in peripheral blood
- Peripheral blood basophils ≤ institutional upper limits of normal
- No extramedullary involvement (including no hepatomegaly or splenomegaly)

2) No Evidence of Leukemia (NEL)
Meet all of the following:

- WBC≤ institutional upper limit of normal
- No blasts or promyelocytes in the peripheral blood

- Bone marrow blasts ≤ 5%
- < 5% myelocytes plus metamyelocytes in the peripheral blood
- Peripheral blood basophils ≤ institutional upper limits of normal
- No extramedullary involvement (including no hepatomegaly or splenomegaly)

And at least one of the following:
a) ANC ≥ 500/mm3 and < 1000/mm3
b) Platelets ≥ 20,000/mm3 and < 100,000/mm3

B) Minor Hematologic Response.
A subject will be determined to have a Minor Hematologic Response if he/she meets all of the following criteria:

- < 15% blasts in bone marrow and < 15% in peripheral blood;
- < 30% blasts + promyelocytes in bone marrow and < 30% blasts plus promyelocytes in peripheral blood;
- < 20% basophils in peripheral blood
- No extramedullary disease other than spleen and liver.
- Confirmed hematologic responses must be confirmed after at least 4 weeks and no concomitant anagrelide or hydroxyurea may have been used during this interval.

Secondary endpoints included duration of OHR, duration of major hematologic response, time to OHR, time to major hematologic response, major cytogenetic response rate, molecular response rates and quality of life measures.

Cytogenetic response criteria are as defined in section 6.1.2.
Determination of molecular response was not included in this interim analysis.

Disease progression:

- Confirmed best hematologic response of MaHR followed by failure to meet MaHR criteria consistently on all assessments over a consecutive 2-week period after starting the maximum dose of dasatinib
- Confirmed best hematologic response of MiHR followed by failure to meet MiHR criteria consistently on all assessments over a consecutive 2-week period after starting the maximum dose of dasatinib
- No decrease from baseline percent blasts in peripheral blood or bone marrow on all assessments over a 4-week period after starting the maximum dose of dasatinib
- The investigator reports that the subject has progressed or died

Withdrawal criteria:

- Study therapy was immediately discontinued for any of the following reasons:
- Withdrawal of informed consent
- Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicated that continued treatment was not in the best interest of the subject

- Disease progression at the highest tolerated dose
- Pregnancy
- Termination of the study by BMS
- Imprisonment or compulsory detention for treatment of either a psychiatric or physical illness (e.g., infectious disease)

Data Set Descriptions:

The following data sets were used:
All treated subjects: all subjects who received at least 1 dose of study drug.

Evaluable subjects for cytogenetic response: All treated subjects who have at least 1 on-study valid cytogenetic assessment (i.e., > 0 metaphases have been reported) or subjects who discontinued for any reason prior to the first on-study valid cytogenetic assessment.

Evaluable subjects for cytogenetic response with at least 20 metaphases: All treated subjects who have at least one on-study valid cytogenetic assessment where ≥ 20 metaphases have been observed or subjects who discontinued for any reason prior to the first on-study valid cytogenetic assessment.

Additionally enrolled subjects: All subjects who were enrolled after 23 May 2005.

Statistical Analyses:
All tables were presented for all treated subjects, lymphoid blast CML subjects, Ph+ ALL subjects, imatinib-resistant subjects, and imatinib-intolerant subjects.

Descriptive statistics (frequency tables) were used to summarize categorical variables (demographic characteristics, safety, laboratory observations, and quality of life measures). Continuous and other numeric variables were summarized by presenting the number of observations, mean, standard deviation, median, minimum, and maximum.

Response rates (hematologic and cytogenetic) were estimated, along with their 95% exact CIs based on the Clopper-Pearson method when the sample was > 5 subjects. Kaplan-Meier estimates of the median time-to and durations of MaHR and OHR were provided along with their 95% CIs. The Kaplan-Meier estimate of the probability curve was also provided.

Efficacy Results:

Reviewer's Table A50. CA180015. Baseline Patient Demographics by Disease

Baseline Parameter	Lymphoid Blast N=42	Ph+ ALL N=36	Total N=78
Gender, n (%)			
Male	22 (52)	23 (64)	45 (58)
Female	20 (48)	13 (36)	33 (42)
Age (years), median (range)	47 (19-72)	46 (15-85)*	47 (15-85)
Age ≥ 65 years, number (%)	6 (14)	6 (17)	12 (15)
Race, n (%)			
White	40 (95)	35 (97)	75 (96)
Black	1 (2)	0 (0)	1 (1)
Asian	1 (2)	1 (3)	2 (3)
ECOG performance status, n (%)			
0	13 (31)	8 (22)	21 (27)
1	18 (43)	16 (44)	34 (44)
2	7 (17)	11 (31)	18 (23)
unknown	4 (10)	1 (3)	5 (6)

* one 15 year-old subject (CA180015-13-15067) received a protocol exemption to participate in the study

Among lymphoid blast (LB) patients, the male: female ratio was approximately 1:1, in contrast to the Ph + ALL population, where nearly 2/3 of subjects were male. Most patients were under 65 and nearly all were white. Most had good ECOG performance status (0-1).

Reviewer's Table A51. CA180015. Baseline Demographic Characteristics, Imatinib Resistant vs. Intolerant

Baseline Parameter	Imatinib resistant N=71	Imatinib intolerant N=7	Total N=78
Gender, n (%)			
Male	40 (56)	5 (71)	45 (58)
Female	31 (44)	2 (39)	33 (42)
Age (years), median (range)	47 (15-85)	44 (26-72)	47 (15-85)
Age ≥ 65 years, number (%)	11 (15)	1 (14)	12 (15)
Race, n (%)			
White	68 (96)	7 (100)	75 (96)
Black	1 (1)	0 (0)	1 (1)
Asian	2 (3)	0 (0)	2 (3)
ECOG performance status, n (%)			
0	19 (27)	2 (29)	21 (27)
1	30 (42)	4 (57)	34 (44)
2	17 (24)	1 (14)	18 (23)
unknown	5 (7)	0 (0)	5 (6)

Disease, n (%)			
Lymphoid blast CML	37 (52)	5 (71)	42 (54)
Ph + ALL	34 (48)	2 (39)	36 (46)

The number of patients in the imatinib intolerant category was small, accounting for only about 10% of study patients. These patients were more likely to be male, and more likely to have LB CML than the imatinib resistant patients. Otherwise, the groups were similar with respect to demographic characteristics.

Disease History:

Reviewer's Table A52. CA180015. Disease History and Prior Therapies Other Than Imatinib

	Lymphoid Blast N=42	**Ph+ ALL N=36**
Time from initial CML diagnosis (months) Median (range)	27.6 (1.7-185.5)	20.0 (3.2-96.8)
Prior bone marrow transplant, n (%)	14 (33.3)	15 (41.7)
Prior chemotherapy, n (%)	33 (78.6)	33 (91.7)
Prior Interferon, n (%)	20 (47.6)	3 (8.3)
Prior hydroxyurea or anegralide, n (%)	33 (78.6)	5 (13.9)
Prior radiotherapy, n (%)	8 (19.0)	12 (33.3)

Patients enrolled in the study had a long history of CML (median 28 months) or Ph+ ALL (median 20 months) at the time of dasatinib initiation. All patients had received imatinib and most had received other anti-leukemic therapies including chemotherapy and/or interferon. As would be expected based on standard treatment of these diseases, patients with LB CML were more likely than patients with Ph + ALL to have received prior interferon, while almost all patients with Ph + ALL had received prior chemotherapy.

Reviewer's Table A53. CA180015. Prior Imatinib Therapy

	Lymphoid Blast N=42	**Ph+ ALL N=36**
Length of Imatinib Therapy, n (%)		
< 1 year	20 (47.6)	16 (44.4)
1-3 years	12 (28.6)	19 (52.8)
> 3 years	10 (23.8)	1 (2.8)
Highest Imatinib Dose, n (%)		
< 400 mg	1 (2.4)	0
400-600 mg	19 (45.2)	19 (52.8)
> 600 mg	22 (52.4)	17 (47.2)
Best Hematologic Response, n (%)		
Complete	28 (66.7)	27 (75.0)
No Evidence of Leukemia	3 (7.1)	0 (0)

No Response	7 (16.6)	3 (8.3)
Unable to Determine	4 (9.5)	6 (16.7)
Best Cytogenetic Response, n (%)		
Complete	14 (33.3)	15 (41.7)
Partial	4 (9.5)	3 (8.3)
Other	24 (57.1)	18 (50)

Slightly more than half of all patients had received imatinib for a year or more. Almost all had received doses of 400 mg or higher. Best hematologic response to imatinib included complete responses in two-thirds of CML patients and three-quarters of ALL patients. One-third of CML lymphoid blast patients achieved a complete cytogenetic response as did over 40% of Ph+ ALL patients.

Reviewer's Table A54. CA180015. Reasons for Imatinib Intolerance

Reason for imatinib intolerance*	N=7
Cytopenias	5
Gastrointestinal symptoms	3
Liver dysfunction	2

* patients may have had more than one reason for imatinib intolerance

Protocol Deviations are described in Table A55.

Reviewer's Table A55. CA180015. Protocol Deviations

	N=78
No lab tests within 72 hours of dosing	73
Received antineoplastic agent within 28 days	31
Baseline lab value out of range	15
Other prohibited medications within time window*	7
No bone marrow tests within 4 weeks of dosing	6
Received interferon or cytarabine within 14 days	3
Received Gleevec within 7 days of dosing**	2
Age < 18	1
Failed Ph+ criteria	1

* includes aspirin within 14 days, drugs associated with torsades de pointes within 5 days
** both patients were granted protocol exceptions due to urgent need to initiate treatment

Most of these protocol deviations for eligibility are in parameters established to ensure patient safety and do not impact the efficacy analysis. The exception is the patient listed as "failed Ph+ criteria" (patient CA 180015-18-15015). No cytogenetic analysis is documented for this patient at screening. However, response to prior imatinib therapy is reported as complete hematologic response and complete cytogenetic response. Two subjects had received imatinib up to 4 days

prior to dasatinib and were granted protocol exceptions by the sponsor due to an urgent need for treatment.

Extent of Exposure

The median duration of therapy was 2.8 months in lymphoid blast CML subjects and 3.2 months in Ph+ ALL subjects. The median of the average daily dasatinib dose was 140 mg for both populations. Thirty-nine (93%) lymphoid blast CML subjects and 31 (86%) Ph+ ALL subjects received > 90% of the planned dasatinib dose.

Hematologic Response

Table A56 summarizes the major hematologic responses (CHR + NEL) and the overall hematologic responses (OHR=MaHR + minor responses)—Sponsor's analysis.

Reviewer's Table A56. CA180015. Hematologic Responses in Patients with Lymphoid Blast CML and Ph + ALL

	CHR N (%)	NEL N (%)	MaHR N (%)	OHR N (%)
Lymphoid Blast (n=42) (95% CI)	11 (26) (3-17)	2 (5) (0.6-16)	13 (31) (18-47)	15 (36) (22-52)
Ph + ALL (n=36) (95% CI)	11 (31) (16-48)	4 (11) (3.1-26)	15 (42) (26-59)	17 (47) (30-65)

Reviewer's analysis:
All the hematologic were verified. The major and overall hematologic response rates were 31% and 36% in the lymphoid blast subjects and 42% and 46% in Ph+ ALL subjects. Complete responses with return of normal peripheral blood counts accounted for two-thirds to three-quarters of the major responses.

The patients who achieve a MaHR are those who are most likely to have benefited from the drug. For this reason, MaHR is viewed as the most relevant endpoint for drug approval in this population. Because MaHR is the most relevant regulatory endpoint, the reviewer focused on this endpoint for further analysis of response and progression data.

Differences in the analysis of dates of progression and/or censoring between the sponsor and the reviewer were sent as a query to the sponsor for an explanation. These differences are summarized in the Table A57.

Table A57. Differences in Assignment of Progression Between Sponsor's Analysis and FDA Review

Subject ID	Sponsor Outcome	Reviewer Outcome	Final Adjudication
0044-15015	Censored 10/26/05	Progression 9/1/05	Progression 9/1/05
0044-15059	Censored 10/18/05	Progression 10/18/05	Progression 10/18/05
0021-15060	Censored 10/12/05	?Progression 8/17/05	Censored 10/12/05

In the case of patient 0044-15015, a Ph+ ALL patient, recurrence of extramedullary disease is documented in the database on 9/1/05. The sponsor reports that this patient had CNS disease which transiently improved on dasatinib, but then recurred on 9/1/05 without evidence of hematologic recurrence. The sponsor believes that since the CNS is a sanctuary site for leukemia, control of CNS disease is not expected, and recurrence in the CNS should not be counted as PD. The patient apparently continued on therapy after that date due to continued hematologic control. The reviewer believes that dasatinib apparently does have activity in the CNS, since disease control at that location did occur, albeit transiently. Recurrence at this site is therefore a progression.

Patient 0044-15059, also a Ph + ALL patient, developed recurrence noted on a bone marrow biopsy on 10/18/05. 88% blasts were noted in the marrow at that time. This was also the last date of assessment in the submitted database. The sponsor reports that at the time of the analysis, information on the discontinuation of treatment was not yet available and so the subject was censored. The sponsor will consider the subject as a progression in subsequent analyses. The reviewer updated this patient to progression based on this information.

Patient 0021-15060, a patient with Ph + ALL, had a best response of NEL. However, this patient had a fluctuating white blood cell (wbc) count which periodically elevated above the upper limit of normal without any evidence of recurrent leukemia. The patient had a two-week period in which the wbc count remained elevated on all assessments; this met the protocol defined criteria for progression. The patient continued on therapy, the wbc count decreased back to the normal range and the patient continued to be without evidence of leukemia. Based on the lack of other data supporting a recurrence, the reviewer agrees with the sponsor's assessment that this patient remains in response and the subject was therefore censored in the duration of response analysis.

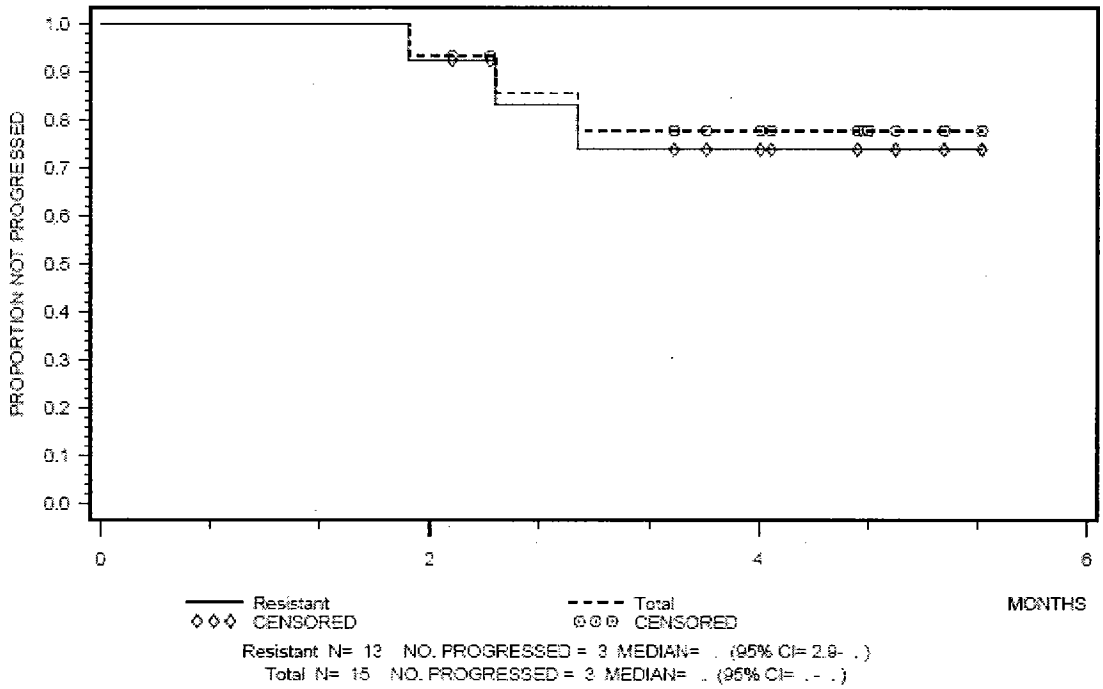
Response Duration:

Sponsor's Analysis:

Duration of response in the 13 lymphoid blast CML subjects with MaHR is displayed in Figure 7 Efficacy). As of the data cutoff, 6 of the 13 subjects had progressed or died. The longest duration of response was 5.4+ months (imatinib-resistant Subject CA180015-23-15046) and the shortest duration of response was 1.6+ months (imatinib-intolerant Subject CA180015-47-15073). The median time to MaHR was 35 days.

Duration of response in the 15 Ph+ ALL subjects with MaHR is displayed in Figure A4. As of the data cutoff, 5 of the 15 subjects had progressed or died. The longest duration of response was 5.4+ months (imatinib-resistant Subject CA180015-13-15012) and the shortest duration of response was 1.9+ months (imatinib-resistant Subject CA180015-103- 15028). The median time to MaHR was 57 days.

Figure A8. Duration of MaHR in Ph+ ALL Subjects—6 month Efficacy update p.90



Reviewer's Analysis:
There are no changes to the sponsor's analysis of duration of response in lymphoid blast patients. With 6/13 progression events, median duration of response in the lymphoid blast population was 3.71 months (95 % CI 2.79, upper limit not reached).
Based on the changes made in two patients in the Ph + ALL population from censored to progressed, the duration of response data were recalculated by the statistical reviewer (Dr. Janet Jiang).

5 of 15 patients (33%) had progressed at the time of the analysis. The median duration of response was 4.83 months (95% CI 2.89, upper limit not reached). The adjusted K-M curve is shown in Figure 6 (Efficacy).

Cytogenetic Responses
Best cytogenetic response for all subjects is listed in Table A58.

Reviewer's Table A58. Best Cytogenetic Response in All Treated Patients

	Ph + ALL 36	Lymphoid Blast N=42
Best Response, n (%)		
Complete (0% Ph+ metaphases)	21 (58)	18 (43)
Partial (>0-35%)	0 (0)	3 (7)
Minor (>35-65%)	1(3)	0 (0)
Minimal (>65-95%)	0 (0)	3 (7)
No response (>95-100%)	0 (0)	4 (10)
Unable to determine	14 (39)	14 (33)
Best Response (based on ≥20 metaphases), n (%)		
Complete (0%)	16 (44)	15 (36)
Partial (>0-35%)	0 (0)	3 (7)
Minor (>35-65%)	0 (0)	0 (0)
Minimal (>65-95%)	0 (0)	1 (2)
No response (>95-100%)	0 (0)	2 (5)
Unable to determine	20 (56)	21 (50)

Cytogenetic response data were unavailable for over one-third of the studied population, and cytogenetic data based on at least 20 metaphases was absent for over half of the patients. In those patients in whom data was available to assess response, most of the responses which occurred were complete cytogenetic responses.

Major cytogenetic response (MCyR) included patients achieving both complete cytogenetic response (no Ph+ metaphases) and partial cytogenetic response (>0-35% Ph+ metaphases). Major cytogenetic response occurred in 50% [95% CI 34-66] of patients with lymphoid blast CML and 58% [95 % CI 41-75] of patients with Ph+ ALL. Major cytogenetic response as assessed in samples with at least 20 metaphases evaluated was 43% in the lymphoid blast population and 44% in the Ph+ ALL population.

Reviewer's Table A59. Percent of Subjects with or without Cytogenetic and Hematologic Responses who Progressed or Died*

	MCyR	No MCyR	MaHR	OHR	No MaHR
Lymphoid Blast	10/21 (48%)	20/21 (95%)	6/13 (46%)	7/15 (47%)	23/27 (85%)
Ph + ALL	9/21 (43%)	9/15 (60%)	5/15 (33%)	7/17 (41%)	15/19 (79%)

* patients listed as without cytogenetic responses include those in whom response could not be determined

Among all patients with MCyR (n=42), 12 (29%) had progressed prior to data cutoff. Among patients who achieved both a MaHR and a MCyR (n=26), 9 (35%) progressed prior to data cutoff.
Among the 21 lymphoid blast subjects who achieved a MCyR, 10 (48%) had progressed; among the 12 lymphoid blast subjects who achieved both a MaHR and a MCyR, 5 (42%) had

progressed. Nearly all patients with LB disease who did not achieve a MCyR progressed or died by the data cutoff date.
Among the Ph + ALL patients who achieved a MCyR (n=21), 9 had progressed (43%); among the 14 patients who achieved both a MaHR and MCyR, 4 (29%) had progressed.

The efficacy of dasatinib by age and gender in patients with lymphoid blast CML and Ph + ALL is described in Table A60. Note that there were not enough non-white patients on the study (n=3) to make any comparisons based on race.

Reviewer's Table A60. Efficacy in Selected Subpopulations—MaHR

	Lymphoid Blast	Ph + ALL
Age		
<65	12/36 (33%)	13/30 (43%)
≥65	1/6 (17%)	2/6 (33%)
Gender		
Male	9/22 (41%)	9/23 (39%)
Female	4/20 (20%)	6/13 (46%)

Reviewer's Conclusions

The efficacy of dasatinib in patients with lymphoid blast CML and Ph + ALL who were resistant to or intolerant of imatinib was evaluated in a single-arm study with major hematologic response as the primary efficacy endpoint. This submission was based on the data available for 78 patients who had received at least six months of follow-up. The starting dose of dasatinib was 70 mg bid. MaHR occurred in 31% [95% CI 18-47%) of LB subjects and in 42% [95% CI 26-59%]. The median duration of response in the lymphoid blast population (based on progression in 6/13 subjects) was 3.71 months (95 % CI 2.79, upper limit not reached). The median duration of response in Ph + ALL (based on progression in 5/15 subjects) was 4.83 months (95% CI 2.89, upper limit not reached). Major cytogenetic response was evaluated as a secondary endpoint and occurred in 50% [95% CI 34-66] of patients with lymphoid blast CML and 58% [95 % CI 41-75] of patients with Ph+ ALL.

10.1.2 Chronic CML. CA180017: Efficacy of Dasatinib vs. Imatinib in Subjects with Chronic CML Resistant to Imatinib

Study status: Study was started on February 10, 2005. Thirty-six subjects at 18 centers worldwide (13 in Western Europe, 2 in Canada, 1 each in USA, Brazil, and Korea) were randomized by June 30, 2005, when enrollment was closed. The study is ongoing.

Study Design: Randomized, open-label, non-comparative Phase 2 study of dasatinib 70 mg BID vs. imatinib 400 mg BID in subjects with chronic phase CML resistant to imatinib 400 mg to 600 mg daily. Eligible subjects were randomized in a 2:1 ratio to receive either dasatinib or imatinib at above doses on a continuous basis. Randomization was stratified by site and cytogenetic

response on prior imatinib therapy (any cytogenetic response [complete, partial, minor, or minimal] vs. no cytogenetic response). Dasatinib dose escalations were allowed in case of disease progression or lack of response, or reductions to manage drug toxicity. No dose escalation was allowed for imatinib. Dose reduction of imatinib to 600 mg/day was allowed, provided the patient had been previously treated at that dose level. Crossover to the alternative treatment was permitted for lack of response, confirmed disease progression or persistent intolerance despite dose reduction, after a washout period of 2 days for dasatinib and of 1 week for imatinib. Cytogenetic assessment was to be performed every 12 weeks and at the time of crossover. Hematologic assessment was to be performed weekly up to 12 weeks and every 2 weeks thereafter.

Primary endpoint: MCyR at 12 weeks.
Secondary endpoints: Durability and time to MCyR; CHR rate, duration, and time to CHR.

Study Population
Key Inclusion Criteria:

- Men and women, 18 years or older, signed informed consent life expectancy of > 12 weeks; ECOG PS 0 -1.
- Has chronic phase CML, defined as < 15% blasts in peripheral blood and in bone marrow, < 20% basophils in peripheral blood, < 30% blasts + promyelocytes in peripheral blood and bone marrow, platelets ≥ 100,000/mm^3 unless thrombocytopenic due to recent therapy, no extramedullary involvement (other than liver or spleen).
- Was not previously treated with imatinib at a dose > 600 mg/day.
- Resistant to imatinib (defined as one of the following): loss of MCyR, loss of CHR, continuously increasing WBC (doubling of WBC from the nadir to ≥ 20,000/mm^3 or an increase by > 50,000/mm^3 above lowest count), no CHR after 12 weeks, no CyR after 24 weeks, and no MCyR after 52 weeks at imatinib doses of 400 to 600 mg/day.
- Able to tolerate imatinib at the highest previously received dose without Grade ≥ 3 imatinib-related non-hematological toxicity and without Grade 4 imatinib-related hematological toxicity lasting > 7 days.
- Adequate hepatic function (total bilirubin ≤ 2.0 x ULN, ALT/AST ≤ 2.5 x ULN).
- Adequate renal function (serum creatinine ≤ 1.5 x ULN).
- Serum K, Mg, Ca WNL.

Key Exclusion Criteria:

- Eligible and willing to undergo transplantation during the screening period.
- Women of childbearing potential who were unwilling or unable to use an acceptable method of pregnancy avoidance for the entire study period of at least 1 month before and for at least 3 months after completion of the study medication.
- Pregnancy, positive pregnancy test on enrollment or prior to study drug administration, or breastfeeding.
- Men whose partners are women of childbearing potential unwilling or unable to use pregnancy avoidance methods for the periods stated above.
- Subjects who have previously described BCR-ABL mutation (a list of mutation is provided).
- Previous accelerated phase or blast crisis CML.

- Intolerance to imatinib: Grade ≥ 3 imatinib-related non-hematological toxicity, Grade 4 imatinib-related hematological toxicity lasting > 7 days, and imatinib-related toxicity that leads to imatinib discontinuation or disruption in dosing > 4 weeks.

Treatments Administered

Dasatinib

Dasatinib was administered daily at an oral dose of 70 mg BID (q.12 h).

- Dose escalation. Dose was to be increased to 90 mg BID in patients with disease progression or failure to achieve a MCyR after 12 weeks of dasatinib, in absence of prohibitive toxicity.
- Discontinuation. Dasatinib was to be discontinued in patients who experience Grade 4 non-hematological toxicities, Grade 3 nausea/vomiting or diarrhea (3rd event) and Grade 3 neuropathy, Grade 3 organ (renal, cardiac, CNS) drug-related toxicities, and QTc ≥ 530 msec.
- Treatment interruption. Treatment could be interrupted for up to 21 days for 2 consecutive QTc ≥ 500 msec and < 530 msec (Day 1 and Day 8), dasatinib-related Grade 2 or 3 non-hematological toxicity, Grade 3/4 neutropenia, and thrombocytopenia of < 50,000/mm^3. Dasatinib was to be discontinued in patients who did not recover from the above toxicities within 21 days.
- Dose de-escalation. A guideline is provided.

Imatinib

Patients randomized to imatinib were treated with imatinib 400 mg BID. No dose escalation was allowed. Dose interruption was allowed for severe non-hematologic adverse reaction, ANC < 1000/mm^3, and platelets < 50,000/mm^3. Dose could be reduced to 600 mg/day. Guidelines for dose modifications were as provided in package insert.

Crossover between arms

Patients in the dasatinib arm who have disease progression despite dose escalation or who have AEs that would preclude additional treatment with dasatinib were offered the opportunity to cross over to the imatinib arm following a 2-day washout period. Patients in the imatinib arm who had no MCyR or ≥ 30% decrease in the percentage of Ph+ metaphases, or showed evidence of disease progression, or had AEs that would preclude additional imatinib treatment were to cross over to dasatinib arm following a 1-week washout period.

Disposition of Study Subjects

Study accrual closed on September 21, 2005 with 166 subjects enrolled. Of the first 36 subjects randomized by June 30, 2005, all received treatment and had at least 12 weeks of follow-up data by October 25, 2005 (data cutoff date for interim analysis). As of October 25, 2005, 20/22 (91%) of the dasatinib arm subjects were still on initial treatment, 2/22 (9%) crossed over to imatinib arm. The reasons for crossover were intolerance (1 subject) and disease progression (1 subject). Three of 14 (21%) imatinib arm subjects were still on treatment, 11/14 (79%) crossed over to dasatinib arm. The reasons for crossover were intolerance (6 subjects), no MCyR (4 subjects), and no MCyR plus disease progression (1 subject).

Population Data Sets

The All Randomized data set includes the 36 randomized subjects and was used for primary efficacy analyses. The All Evaluable data set includes 31 subjects (17 dasatinib, 14 imatinib). Four dasatinib subjects did not meet eligibility criteria and one subject had no valid cytogenetic assessment at 12 weeks.

Demographic and Baseline Characteristics

The subjects in both treatment groups were balanced with respect to age, race, and ECOG PS scores, as shown in Reviewer's Table 59 below (from Sponsor's Table 5.3). Balance was not achieved with respect to gender. Males and females were equally represented in the dasatinib arm, but 13/14 subjects in the imatinib arm were females.

Reviewer's Table A61. CA180017. Demographic characteristics

Characteristic	Dasatinib, N = 22	Imatinib, N = 14
Age, years		
Mean ± SD	53 ± 15.7	52 ± 14.9
Median (min – max)	57 (24 – 76)	56 (28 – 69)
21-45 years	6 (27.3%)	4 (28.6%)
46-65	10 (45.5%)	6 (42.9%)
66-75	5 (22.7%)	4 (28.6%)
> 75	1 (4.5%)	0
Gender		
Male	11 (50%)	1 (7.1%)
Female	11 (50%)	13 (92.9%)
Race		
White	20 (90.9%)	13 (92.9%)
Black/African American	1 (4.5%)	1 (7.1%)
Asian	1 (4.5%)	0
ECOG PS		
0	14 (63.6%)	8 (57.1%)
1	8 (36.4%)	5 (35.7%)
Not reported	0	1 (7.1%)

Disease characteristics at baseline are shown in Reviewer's Tables A62 and A63 below (from Sponsor's Tables 5.4.1A, B). Subjects in both groups had a long history of CML (median time since diagnosis was more than 5 years in both treatment arms) and were extensively pretreated. The two treatment groups were balanced with respect to previous cancer therapies (imatinib, hydroxyurea, anagrelide, interferon and chemotherapy agents). There was an imbalance for history of stem cell transplant (5 such subjects in the dasatinib arm and none in the imatinib arm).

Reviewer's Table A62. CA180017. Baseline Disease and Previous CML Therapy Characteristics

Characteristic	Dasatinib, N = 22	Imatinib, N = 14
Time from initial diagnosis (months)		
Median (min – max)	60.9 (5.6 – 124.5)	61.2 (15.4 – 132.6)
Length of imatinib therapy, no. of subjects (%)		
< 1 year	1 (4.5%)	0
1 – 3 years	8 (36%)	7 (50%)
> 3 years	13 (59%)	7 (50%)
Highest dose		
400 mg/day	5 (23%)	2 (14%)
500 mg/day	1 (4.5%)	0
600 mg/day	16 (73%)	12 (86%)
Best hematologic response to imatinib		
CHR	19 (86%)	14 (100%)
Stable	3 (14%)	0
Best cytogenetic response to imatinib		
CCyR	8 (36%)	1 (7%)
PCyR	1 (4.5%)	2 (14%)
Minimal CyR	3 (14%)	2 (14%)
Minor CyR	2 (9%)	1 (7%)
Stable (no response and no progression)	8 (36%)	7 (50%)
Progression		1 (7%)
Previous other therapy (no. of subjects, %)		
Bone marrow transplant	5 (23%)	0
Radiotherapy	0	0
Chemotherapy	7 (32%)	8 (57%)
Interferon	14 (64%)	11 (79%)
Hydroxyurea or anagrelide	22 (100%)	12 (86%)

About half the subjects in both groups had received more than 3 years of prior imatinib therapy, during which 19/22 (86%) of dasatinib arm subjects and 14/14 (100%) of imatinib subjects had achieved a CHR. Nine of 22 (41%) dasatinib arm subjects and 3/14 (21%) imatinib arm subjects had achieved a MCyR.

Reasons for imatinib resistance in both treatment groups are shown in the Reviewer's Table (Sponsor's Table S.3.3.1) below. The largest categories were failure to achieve MCyR after 12 months of therapy with 400 to 600 mg/day of imatinib, and failure to achieve any cytogenetic response after 6 months of therapy.

Reviewer's Table A63. CA180017. Reasons for Imatinib Resistance

Reason for imatinib resistance	Dasatinib N = 22	Imatinib N = 14	Total N = 36
Failure to achieve MCyR after 12 months	8 (36%)	8 (57%)	16 (44%)
Failure to achieve any CyR after 6 months	7 (32%)	5 (36%)	12 (33%)
Failure to achieve CHR after 3 months	2 (9%)	0	2 (6%)
Loss of MCyR	6 (27%)	3 (21%)	9 (25%)
Loss of CHR	5 (23%)	3 (21%)	8 (22%)
Increasing WBC count	1 (5%)	0	1 (3%)

Baseline hematologic disease status is shown in Reviewer's Table A64 (data from Sponsor's Table 5.4.1C) . According to the Sponsor, baseline hematologic values, such as basophilia in peripheral blood, WBC and PNN counts, platelets, hemoglobin were consistent with chronic phase CML, except in one subject who had accelerated phase CML (32% promyelocytes and 10% blast cells in bone marrow). All other subjects had < 15% blast cells in the bone marrow.

Reviewer's Table A64. CA180017. Baseline Hematologic Disease Status

Characteristic	Dasatinib, N = 22	Imatinib, N = 14
WBC median (min – max) < 20,000/mm³ ≥ 20,000/mm³	9,700/mm³ (3,100 – 95,400) 19 subjects (86%) 3 subjects (14%)	6,300 (1,800 – 43,500) 12 subjects (86%) 2 subjects (14%)
Basophils in PB No. of subjects (%) Median (min – max)	 13 (59%) 2% (0% – 14%)	 8 (57%) 1.9% (0% – 8%)
Platelet count, median (min – max)	289,000/mm³ (97,000 – 1,903,000)	261,500/mm³ (89,000 – 547,000)
Hgb, median (min – max)	11.9 g/dL (9.9 – 15.0)	12.0 g/dL (9.0 – 16.0)
Involvement of spleen, liver, nodes, other organs	0	0

Two dasatinib subjects had thrombocytopenia < 100,000/mm³ due to prior imatinib treatment and prior hydroxyurea. One subject had Grade 3 leukopenia and Grade 3 neutropenia due to prior imatinib treatment.

Reviewer's Notes:
1. Only one-third of the subjects had elevated WBC counts, and only about one-half had early neutrophil precursors in peripheral blood (Reviewer's Table 63 , data from Patient Profiles, Appendix 4.1). Ten subjects were leukopenic (1,800 – 4,900/mm³), 14 had normal WBC count (5,000 – 10,000/mm³), and 12 had elevated WBC (12, 300 – 95,400/ mm³). The median percentage of bone marrow blasts was 2% (range, 0% to 10%).

Reviewer's Table A65. CA180017. Baseline Hematologic Disease Status – WBC and Differential Counts

	Dasatinib, N = 22	*Imatinib, N = 14*
WBC counts/ mm³		
< 5,000	*4 (18%)*	*6 (43%)*
5,000 – 10,000	*10 (45%)*	*4 (29%)*
> 10,000	*8 (36%)*	*4 (29%)*
PMN precursors present	*14 (64%)*	*7 (50%)*
Normal differential	*4 (18%)*	*3 (21%)*
No differential at start of therapy	*4 (18%)*	*4 (29%)*

2. The main reason for treating these chronic phase CML patients was cytogenetic characteristics. Thirty-three (33) of the 36 were treated because of Ph+ cytogenetics. One subject was Ph-, but was positive on FISH. Two Ph- patients were treated because they were considered to be at high risk for developing Ph+ cytogenetics; they were Ph- at the start of treatment and stayed Ph- during treatment (subjects 0044-17002 and 0100-17028).

Extent of Exposure

The extent of exposure is summarized in Reviewer's Table (from CA1800017 Report Table 6.1). The median average daily doses of dasatinib (140 mg/day) and of imatinib (788 mg/day) were equal or close to the target dose. Most of the patients in both treatment arms received 90% - 100% of the target dose. However, while most 86% of the patients in the dasatinib arm (86%) were treated for more than 3 months, most of the imatinib arm patients (79%) were treated for 3 months or less.

Reviewer's Table A66. CA180017. Dose Intensity and Duration of Treatment

	Dasatinib, N = 22	**Imatinib, N = 14**
Daily dose, median (min – max)	**140.0 (64 – 166)**	**787.5 (623 – 800)**
Percentage of dose administered		
< 90%	8 patients (36%)	3 (21%)
> 90 -100%	13 (59%)	11 (79%)
> 100%	1 (4.5%)	0
Duration of treatment		
Median no. months (min – max)	3.71 (1.38 – 6.47)	2.74 (0.16 – 3.68)
Patients treated for		
≤ 3 months	3 patients (14%)	11 patients (79%)
3 – 6 months	17 (77%)	3 (21%)
> 6 months	2 (9%)	0

Discontinuation of Study Therapy/Crossovers to the Alternate Treatment Arm

None of the subjects in either treatment group discontinued from the study. The numbers of subjects who crossed over to the alternate arm and the reasons for crossovers are listed below.

Dasatinib arm to imatinib arm: disease progression (1 subject), intolerance (grade 4 neutropenia and pneumonia) (1 subject).
Imatinib arm to dasatinib arm: no MCyR (4 subjects), no MCyR with disease progression (1 subject), 6 subjects with intolerance, which consisted of Grade 3 thrombocytopenia + Grade 3 neutropenia (1), Grade 3 fatigue + Grade 3 neutropenia (1), Grade 4 joint effusion (1), Grade 2 vomiting despite dose reduction (1), Grade 3 myalgia (1), and Grade 2 recurrent dermatitis with blisters on lower legs (1).

Dose Reductions, Interruptions, and Escalations

- Eight subjects in the dasatinib arm and one subject in the imatinib arm had dose reductions.
- Nine dasatinib arm subjects and 4 imatinib arm subjects had dose interruptions. The most common reason for dose reductions and interruptions was hematological toxicity.
- One dasatinib arm subject had the dasatinib dose increased to 90 mg BID because of disease progression. Two others had dose increased to 70 mg BID after a dose reduction to 50 mg BID.

Efficacy Results

Primary Efficacy Endpoint: Cytogenetic Response

Cytogenetic response data, according to Sponsor's Table 7.2A, are shown in Reviewer's Table A7 . MCyR rate at 12 weeks, the primary endpoint, was 45% in the dasatinib group and 21% in the imatinib group. The difference in MCyR rates was 24% (95% CI: - 9.9 to +51.2) with dasatinib group rate about double that of imatinib group.

Seven of 22 (32%) dasatinib subjects and 1/14 (7%) imatinib subjects achieved CCyR.

Reviewer's Table A67. CA180017. Cytogenetic Response at 12 Weeks – All Randomized Subjects

Response	Dasatinib, N = 22	Imatinib, N = 14
Complete (0% Ph+)	7 (32%)	1 (7%)
Partial (>0% - 35% Ph+)	3 (14%)	2 (14%)

The results in the Evaluable Subject population (Sponsor's Table 7.2B) are shown in Reviewer's Table A68. The MCyR rates were 47% in the dasatinib arm and 21% in the imatinib arm.

Reviewer's Table A68. CA180017. Cytogenetic Response at 12 Weeks – Evaluable Subjects (Sponsor's Table)

Response	Dasatinib, N = 17	Imatinib, N = 14
Complete (0% Ph+)	5 (29%)	1 (7%)
Partial (>0% - 35% Ph+)	3 (18%)	2 (14%)

Reviewer's Notes: The data in Patient Profiles (Appendix 4.1) show that in the dasatinib arm 5 subjects had a CCyR (5-17026, 31-17003, 44-17007, 95-17018, and 145-17012) and 3 patients had a PCyR (31-17013m 44-17004, and 94-17024). Thus, the MCyR rate was 36% in the subjects randomized to the dasatinib arm. Response could not be evaluated in 4 patients. The response in 4subjects could not be evaluated for the following reasons: 3 patients in the dasatinib arm were Ph- at study entry (19-17011, 44-17002, and 100-17028), and one patient (100-17029) had no cytogenetic data after the baseline value. The subjects who were Ph- at baseline remained Ph- after 12 weeks of dasatinib therapy. Ten patients had no response, one of them (69-17020) had accelerated phase CML not chronic phase CML.

In the imatinib arm, one subject had a CCyR (145-17017) and two had a PCyR (32-17033 and 42-17025) for a MCyR rate of 21%. Response could not be evaluated in 3 patients for the following reasons: 1 subject had no cytogenetic data after baseline (80-17027) and 2 patients had no cytogenetic data at the time of crossover to the dasatinib arm (44-17004 and 80-17027). Eight patients had no response.

After crossover, one imatinib patient had a PCyR on dasatinib. Other patients had not had 12 weeks of treatment with dasatinib before data cutoff date.

Reviewer's analysis of cytogenetic response data are presented in Table A69.

Reviewer's Table A69. CA180017. Cytogenetic Response at 12 Weeks – All Randomized Subjects (Reviewer's Analysis)

Response	*Dasatinib, N = 22*	*Imatinib, N = 14*
MCyR (CCyR + PCyR)	*8 (37%)*	*3 (21%)*
---Complete (0% Ph+)	*5 (23%)*	*1 (7%)*
---Partial (>0% - 35% Ph+)	*3 (14%)*	*2 (14%)*

Cytogenetic response data after crossovers is limited, because of the short follow-up after crossover. One of 11 imatinib patients had a PCyR at 3 months and 2 had no CyR. Neither of 2 dasatinib arm patients had been treated for 12 weeks; one of them had progressive disease.

Secondary Efficacy Endpoint: Hematologic Response

According to the Sponsor's analysis, 21/22 (95%) subjects in the dasatinib arm and 13/14 (93%) subjects in the imatinib arm had a CHR at 12 weeks. The subject without a CHR in the dasatinib

arm had disease progression by Day 83, crossed over to the imatinib arm and continued to have disease progression on imatinib. The subject in the imatinib arm who crossed over to dasatinib arm on Day 6 had non-hematological toxicity. The subject had a CHR and had no CyR at 12 weeks.

Reviewer's Table A70. CA180017. Hematologic Response at 12 Weeks – All Randomized Subjects

Response	Dasatinib, N = 22	Imatinib, N = 14
Complete Hematologic Response	21 (95%)	13 (93%)

Reviewer's Notes: Review of the data in Patient Profiles (Appendix 4.1) showed that about one-half of the subjects in both arms had normal hematological profiles at baseline (i.e. meeting the criteria for CHR). Therefore, the results of the hematologic response should be presented as in Reviewer's Table A71 below.

Reviewer's Table A71. CA180017. Hematologic Response at 12 Weeks – All Randomized Subjects (Reviewer's Analysis)

	Dasatinib, N = 22	*Imatinib, N = 14*
Number of subjects meeting CHR criteria at baseline	*11/22 (50%)*	*8/14 (57%)*
Number of subjects meeting CHR criteria at 12 weeks	*21/22 (95%)*	*13/14 (93%)*

The duration of CHR could not be estimated. However, 2 of the patients in the dasatinib arm and 6 of the patients in the imatinib arm lost CHR during the period of follow-up. The losses of CHR occurred after 63 and 98 days of dasatinib therapy, and after 49, 51, 82, 83, 91, and 100 days of imatinib therapy. None of these patients had a CyR.

Other Secondary Efficacy Endpoints:

- Durability of MCyR could not be evaluated because follow-up before data cutoff was too short.
- Time to MCyR could not be evaluated because the first cytogenetic analysis was carried out at about 12 weeks. Responses that occurred before 12 weeks would not have been detected.
- Durability of CHR could not be evaluated because follow-up before data cutoff was too short.
- Median time to CHR is stated by the sponsor as 15 days with the cautionary statement that the earliest confirmed CHR, according to protocol, could occur not earlier than 14 days, when the CHR was confirmed.

Reviewer's Summary Statements of CA180017:

- *The sponsor attempted to define a comparator arm for dasatinib by raising the imatinib dose to 400 mg BID. The attempt was not successful, because 79% of patients left the imatinib arm within 12 weeks, either because of intolerance or lack of efficacy.*
- *Dasatinib is clearly an effective drug in patients who cannot tolerate imatinib or who have become imatinib-resistant. The cytogenetic response to dasatinib in this small trial was about 47% (in both ITT and Evaluable populations) as compared to 21% response rate in the high-dose imatinib population.*
- *The cytogenetic response was easily assessed by the Ph+ cytogenetic marker. This study did not define the time to cytogenetic response. Neither did it define the durability of the response. There were no losses of cytogenetic response, but the follow-up period was very short.*
- *In contrast to the cytogenetic response rates, the hematologic response rates were very high and virtually same in both dasatinib and imatinib treatment arms. Hematologic responses occurred rapidly (median of about 15 days). The duration could not be estimated, because of the short follow-up period. However, 2 patients in the dasatinib arm and 6 patients in the imatinib arm, none of whom had a CyR, lost CHR during the follow-up period.*

APPEARS THIS WAY
ON ORIGINAL

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